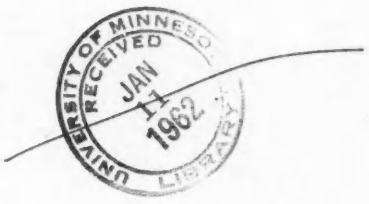
pam-75

TRANSACTIONS OF THE AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS

VOL. LIII 1961



Copies of the 1961 Transactions as well as a limited number of back issues of the Transactions may be obtained from Mr. Vernon J. Miller, 319 S. Smallwood St., Baltimore 23, Md. The price is $5.50 including postage, payable in advance.

Many of the words appearing in the Transactions are proprietary names even though no reference to this fact is made in the text. The appearance of any name without designation as proprietary is therefore not to be regarded as a representation by the American Association of Genito-Urinary Surgeons that it is not a proprietary name or is not the subject of proprietary rights.

S 610.6
Am3g

OFFICERS, 1960–1961*

President

DR. CARL RUSCHE, Los Angeles, Calif.

Vice-President

DR. GEORGE C. PRATHER, Brookline, Mass.

Secretary-Treasurer

DR. WILLIAM J. ENGEL
2020 East 93rd St., Cleveland 6, Ohio

Members of the Council

DR. REED M. NESBIT, Ann Arbor, Mich.
DR. DAVID M. DAVIS, Haverford, Pa.

HONORARY MEMBERS

DR. WILLIAM F. BRAASCH (Nelle) (1913) Mayo Clinic, 102 Second Avenue, S. W., Rochester, Minn.
DR. FRANK HINMAN (Mittie) (1920)
Res: 74 Atherton Avenue, Atherton, Calif.
DR. JOSEPH F. MCCARTHY (Katherine) (1924)
Res: 353 West 57th Street, Apt. 1822, New York 19, N. Y.
DR. GEORGE G. SMITH (Ruth) (1916)
Res: 136 Myrtle Street, Boston 14, Mass.
†DR. ALEXANDER R. STEVENS (1916)
Res: Alstead, New Hampshire
DR. GILBERT J. THOMAS (Ethel) (1923) 2200 Santa Monica Blvd., Santa Monica, Calif.
Res: 9610 Highland Gorge Drive, Beverly Hills, Calif.

CORRESPONDING MEMBERS

DR. PAULO FREDERICO DE ALBUQUERQUE (Arminda) (1955) Rua Assembleia, 51-11°, Rio de Janeiro, Brazil
Res: Avenida Atlantica, 538/601, Rio de Janeiro, Brazil
MR. DAVID BAND (Betty) (1953) 16 Randolph Crescent, Edinburgh 3, Scotland
DR. PIERRE BOUTEAU (1955) 24 Rue Ampere, Paris 17, France
DR. EDUARDO CASTRO (1955) Uruguay 90, Mexico, D. F.
DR. RAUL LOPEZ ENGELKING (Maria Cristina) (1956) Plaza de los Ferrocarrilles No. 3-8 floor, Mexico City 4, D. F.
Res: Sierra Guadarrama 145, Lomas, Mexico City
PROF. BERNARD FEY (Louise) (1953) Hospital Cochin, Paris, France
Res: 54 Avenue de New York, Paris, France
DR. GUSTAVE GIERTZ (Ulla) (1955) Karolinska sjukhuset, Stockholm 60, Sweden
Res: Sveastigen 6, Djursholm, Sweden
PROF. JOHN HELLSTROM (Sonja) (1955) Karolinska sjukhuset, Stockholm, Sweden
Res: Nybrogatan 6, Stockholm, Sweden
MR. KEITH KIRKLAND (1948) 137 Macquarie Street, Sydney, Australia
PROF. RENE KUSS (1955) 152 Avenue Victor-Hugo, Paris 16, France
MR. T. J. MILLIN (1953) 31 Queen's Gate, London, S. W. 7, England
MR. HENRY MORTENSEN (1948) Box 2, Mt. Martha, Victoria, Australia
MR. E. R. REAY (1955) "Harley" 137 Cambridge Terrace, Christchurch, New Zealand
SIR E. W. RICHES (1953) 22 Weymouth Street, London W. 1, England
MR. J. G. SANDREY (1955) St. Peters Hospital, Covent Garden, London W. C., England
DR. ARMANDO TRABUCCO (1954) 1917 Rivadavia, Buenos Aires, Argentina
DR. AQUILINO VILLANEUVA (1954) Av. Oaxaca No. 32, Mexico 7, D. F.
DR. EGON WILDBOLZ (1953) 25 Sulgeneckstrasse, Berne, Switzerland

FELLOWS

DR. HERMAN C. BUMPUS (Helen) (1923)
Res: 1 Upland Road, Duxbury, Mass.
DR. C. E. BURFORD (1926) 958 Arcade Bldg., St. Louis 1, Missouri
Res: 6655 Waterman, University City 30, Mo.

---

*Annual meeting held at the Desert Inn, Las Vegas, Nevada, May 17–19, 1961.
† Died February 3, 1961.

Dr. Edgar Burns (Helen) (1944) Ochsner Clinic, 3503 Prytania St., New Orleans, La.
Res: 1321 State Street, New Orleans 15, La.
Dr. Meredith F. Campbell (Lyn) (1941) 1501 South Miami Avenue, Miami 36, Florida
Res: Same
Dr. Grayson Carroll (Thelma) (1950) 3720 Washington Blvd., St. Louis 8, Missouri
Res: 13 Kingsbury Place, St. Louis, Missouri
Dr. Donald A. Charnock (Gretta) (1949) 2010 Wilshire Blvd., Los Angeles 57, Calif.
Res: 2559 Aberdeen Avenue, Los Angeles 27, Calif.
Dr. Fletcher H. Colby (Jean) (1931) 262 Beacon Street, Boston 16, Mass.
Res: 27 Chestnut Street, Brookline 46, Mass.
Dr. J. A. C. Colston (Harriet) (1921) Johns Hopkins Hospital, Baltimore 5, Md.
Res: Gibson Island, Maryland
Dr. David M. Davis (Betty) (1939) 208 Haverford Square Bldg., Haverford, Pa.
Res: 818 Pennstone Road, Bryn Mawr, Pa.
Dr. Archie L. Dean (Ella) (1935) 30 E. 40th Street, New York 16, N. Y.
Res: 25 Leland Avenue, Pleasantville, N. Y.
Dr. Clyde Deming (Evelyn) (1928) 789 Howard Avenue, New Haven, Conn.
Res: 2 Marshall Road, Hamden 14, Conn.
Dr. George W. Fish (Elise "Lee") (1938) 755 Park Avenue, New York 21, N. Y.
Res: 150-10 Powells Cove Blvd., Whitestone 57, N. Y.
Dr. Roger C. Graves (Hazel) (1924) 12 Bay State Road, Boston 15, Mass.
Res: 107 Dean Road, Brookline 46, Mass.
Dr. Homer G. Hamer (Maone) (1923) 1711 Capitol Avenue, Indianapolis 7, Ind.
Res: 5434 N. New Jersey Street, Indianapolis 20, Ind.
Dr. Alexander B. Hepler (Carolyn) (1936)
Res: Route 1, Box 1284, Bainbridge Island, Washington
Dr. William P. Herbst, Jr. (Catherine) (1940) 1801 Eye Street, N. W., Washington 6, D. C.
Res: 4615 Cathedral Avenue, N. W., Washington 16, D. C.
Dr. George F. Hoch (Florence) (1940) 115 E. 61st Street, New York 21, N. Y.
Res: 1901 Dorchester Road, Brooklyn 26, N. Y.
Dr. T. Leon Howard (Susan) (1936) 1224 Republic Bldg., Denver, Colorado
Res: 721 Emerson Street, Denver, Colorado
Dr. Edward J. McCague (Margaret) (1934) Mercy Hospital, Pittsburgh 19, Pa.
Res: 510 Dorseyville Road, Pittsburgh 38, Pa.
Dr. Vincent J. O'Conor (Katharine "Pete") (1926) 251 E. Chicago Avenue, Chicago 11, Illinois
Res: 179 Lake Shore Drive, Chicago 11, Illinois
Dr. John K. Ormond (Charlotte) (1939) 880 Woodward Avenue, Pontiac, Michigan
Dr. Carl Rusche (1937) Suite 201, 1400 N. Vermont Avenue, Los Angeles, Calif.
Dr. A. J. Scholl (Dorothy) (1926) 1930 Wilshire Blvd., Los Angeles 57, Calif.
Res: 1536 Club View Drive, Los Angeles 24, Calif.
Dr. Winfield W. Scott (Della) (1949) 277 Alexander Street, Rochester 7, N. Y.
Res: 340 Sandringham Road, Rochester 10, N. Y.
Dr. Fedor L. Senger (Frances) (1944)
Res: 279 Southdown Road, Huntington, N. Y.
Dr. Ira Sisk (Freddie) (1929) 1 S. Pinckney Street, Madison 3, Wisconsin
Res: Verona, Wisconsin
Dr. Parke G. Smith (Iva) (1939) 2424 Coral Way, Miami, Florida
Res: 3801 Granada Blvd., Coral Gables, Florida
Dr. W. H. Toulson (Helen) (1938) 101 W. Read Road, Baltimore 1, Maryland
Res: 5403 Falls Road Terrace, Baltimore 10, Maryland

ACTIVE MEMBERS

Dr. Carl Aberhart (Drena) (1948) 1012 Medical Art Bldg., Toronto, Ontario, Canada
Res: 36 Castlefrank Road, Toronto, Ontario, Canada
Dr. Edwin P. Alyea (Nancy) (1958) Duke University Hospital, Durham, N. Carolina
Res: 3102 Devon Road, Hope Valley, Durham, N. Carolina
Dr. George Austen, Jr. (Langhorne) (1960) 203 Commonwealth Avenue, Boston 16, Mass.
Res: 195 Fisher Avenue, Brookline 46, Mass.
Dr. William H. Boyce (Doris) (1957) Bowman Gray School of Medicine, Winston-Salem 7, N. C.
Res: 939 N. Stratford Road, Winston-Salem. N. C.
Dr. George J. Bulkley (Patricia "Pat") (1960) 251 E. Chicago Avenue, Chicago 11, Illinois
Res: 40 Woodley Road, Winnetka, Illinois
Dr. Raymond G. Bunge (Elizabeth "Betty") (1959) University Hospitals, Iowa City, Iowa
Res: 829 Kirkwood Avenue, Iowa City, Iowa
Dr. Edward W. Campbell (Dorothy) (1944) Abington Memorial Hospital, 1200 York Rd., Abington, Penn.
Res: 2300 Washington Lane, Huntingdon Valley, Penn.
Dr. Richard Chute (Ruth) (1947) Veterans Admin. Hospital, 1500 S. Huntington Ave., Boston 30, Mass.
Res: 78 Upland Road, Brookline 46, Mass.

Dr. Justin Cordonnier (Jane) (1955) 4960 Audubon Avenue, St. Louis 10, Missouri
Res: 6306 Washington Avenue, St. Louis 30, Missouri

Dr. C. D. Creevy (Alice) (1939) University Hospital, 412 Delaware St., Minneapolis 14, Minn.
Res: 1633 E. River Road, Minneapolis 14, Minn.

Dr. Ormond S. Culp (Helen) (1948) Mayo Clinic, 200 First Street, S. W., Rochester, Minn.
Res: 1032 Plummer Circle, Rochester, Minn.

Dr. John E. Dees (Susan) (1953) Duke Hospital, Durham, North Carolina
Res: 413 Carolina Circle, Durham, North Carolina

Dr. James H. DeWeerd (Marijane) (1960) Mayo Clinic, 200 First Street, S. W., Rochester, Minn.
Res: 933 - 10th Street, S. W., Rochester, Minn.

Dr. John L. Emmett (Erma) (1944) Mayo Clinic, 200 First Street, S. W., Rochester, Minn.
Res: 617 - 9th Avenue, S. W., Rochester, Minn.

Dr. William J. Engel (Molly) (1937) Cleveland Clinic, 2020 E. 93rd Street, Cleveland 6, Ohio
Res: 12546 Cedar Road, Cleveland 6, Ohio

Dr. Rubin Flocks (1954) University Hospitals, Iowa City, Iowa
Res: 514 Grandview Court, Iowa City, Iowa

Dr. Robert A. Garrett (Betty) (1960) Indiana University Medical Center, 1100 W. Michigan Street, Indianapolis, Ind.
Res: 95 Wellington Road, Indianapolis, Ind.

Dr. Thomas E. Gibson (Jeannette) (1947) 450 Sutter Street, San Francisco 8, Calif.
Res: 145 Laurel Street, San Francisco 18, Calif.

Dr. Willard Goodwin (Mary Joe) (1957) University of California Medical Center, Los Angeles 24, Calif.
Res: 254 Bronwood Avenue, Los Angeles, Calif.

Dr. Frank C. Hamm (Lisbeth) (1942) State University of New York, 450 Clarkson Avenue, Brooklyn 3, New York
Res: 77 Columbia Heights, Brooklyn, N. Y.

Dr. John R. Hand (Vera) (1952) 1216 S. W. Yamhill Road, Portland 5, Oregon
Res: 4915 S. W. Patton Road, Portland 1, Oregon

Dr. J. Hartwell Harrison (Gertrude) (1951) Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Mass.
Res: 68 Dudley Street, Brookline 46, Mass.

Dr. B. Marvin Harvard (Anne) (1957) 789 Howard Avenue, New Haven 4, Conn.
Res: 105 Spring Glen Terrace, Hamden, Conn.

Dr. Norris J. Heckel (Eileen) (1938) 122 S. Michigan Avenue, Chicago 3, Ill.
Res: 20 E. Cedar Street, Chicago, Ill.

Dr. Daniel Riggs Higbee (Olivia) (1950) 1612 Tremont Place, 1117 Republic Bldg., Denver 2, Colorado
Res: 330 Franklin Street, Denver 18, Colorado

Dr. Charles C. Higgins (1933) Cleveland Clinic, 2020 E. 93rd Street, Cleveland 6, Ohio
Res: Wade Park Manor, Cleveland 6, Ohio

Dr. Frank Hinman, Jr. (Marion) (1954) University of California Medical Center, 384 Post Street, San Francisco 8, Calif.
Res: 1000 Francisco Street, San Francisco 9, Calif.

Dr. Clarence V. Hodges (Pha) (1959) University of Oregon Medical School, 3181 S. W. Sam Jackson Park Road, Portland 1, Oregon
Res: Rt. 1, Box 175, West Linn, Oregon

Dr. Robert S. Hotchkiss (Olivia) (1948) 65 East 66th Street, New York 21, N. Y.
Res: 263 Corona Ave., Pelham, N. Y.

Dr. P. Boland Hughes (Anne) (1942) 1323 Medical Arts Bldg., Philadelphia 2, Pa.
Res: 419 Hillbrook Road, Bryn Mawr, Pa.

Dr. Hugh Judge Jewett (Rosalind) (1943) 1201 N. Calvert Street, Baltimore 2, Maryland
Res: 5603 Waycrest Lane, Baltimore 10, Maryland

Dr. Joseph H. Kiefer (Marie) (1950) 25 E. Washington Street, Chicago 2, Illinois
Res: 1240 W. North Shore Avenue, Chicago 26, Ill.

Dr. Willoughby Kittredge (Ruth) (1953) 3503 Prytania Street, New Orleans, La.
Res: 5801 St. Charles Avenue, New Orleans, La.

Dr. John K. Lattimer (Jamie) (1953) Columbia University Medical School, New York 32, N. Y.
Res: 56 Beech Road, Englewood, N. J.

Dr. Wyland F. Leadbetter (Lois) (1948) Massachusetts General Hospital, Fruit Street, Boston 14, Mass.
Res: 166 Marlborough Street, Boston, Mass.

Dr. Robert Lich, Jr. (Edna) (1951) 801 Heyburn Bldg., Louisville 2, Kentucky
Res: Indian Hills, Louisville 7, Kentucky

Dr. Ben D. Massey (Eileen) (1944) 112 N. Madison Avenue, Pasadena, California
Res: 1035 Fallen Leaf Road, Arcadia, Calif.

Dr. Samuel A. MacDonald (Bodine) (1951) 1414 Drummond Street, Montreal, Quebec, Canada
Res: Aberdean Avenue, Westmount, Quebec, Canada

Dr. John T. MacLean (Elizabeth "Betty") (1951) 202 Medical Arts Bldg., Montreal, Quebec, Canada
Res: 599 Victoria Avenue, Westmount, Quebec, Canada

Dr. Donald F. McDonald (Virginia) (1957) University of Rochester Medical Center, 260 Crittenden Blvd., Rochester 20, N. Y.
Res: 239 Sandringham Road, Rochester, N. Y.

Dr. James H. McDonald (Dorothy) (1960) University of Illinois College of Medicine 840 South Wood Street, Chicago 12, Illinois
Res: 5616 Quincy Street, Hinsdale, Illinois

Dr. Reed M. Nesbit (Mabel) (1936) 1313 East Ann Street, Ann Arbor, Michigan
Res: 815 Berkshire, Ann Arbor, Michigan

Dr. Myron N. Nourse (Dorothy) (1959) 1711 N. Capitol Avenue, Indianapolis 7, Indiana
Res: 8064 Morningside Drive, Indianapolis 20, Indiana

* Dr. Louis Orr, Jr. (Dorothy) (1941) 1300 South Orange Avenue, Orlando, Florida
Res: 750 Gatlin Avenue, Orlando, Florida

Dr. John F. Patton (Marjorie) (1949) Walter Reed Army Hospital, Washington 12, D. C.
Res: 6934 - 15th Street, N. W., Washington 12, D. C.

Dr. Eugene F. Poutasse (Arline) (1959) Cleveland Clinic, 2020 E. 93rd St., Cleveland 6, Ohio
Res: 2738 Euclid Heights Blvd., Cleveland, Ohio

Dr. George C. Prather (Marion) (1938) 1180 Beacon Street, Brookline 46, Mass.
Res: 11 Oakcliff Road, Wellesley Hills 81, Mass.

Dr. Charles L. Prince (Kay) (1960) 2515 Habersham Street, Savannah, Georgia
Res: 20 East 52nd Street, Savannah, Georgia

Dr. John N. Robinson (Sylvia) (1947) 11 Earle Avenue, Easton, Maryland
Res: Widgeon Point, Easton, Maryland

Dr. Luis A. Sanjurjo (Guillermina) (1954) Mimiya Hospital, 303 de Diego Ave., Santurce, Puerto Rico
Res: 169 Parque Street, Santurce, Puerto Rico

Dr. William Wallace Scott (Jessie) (1951) Johns Hopkins Hospital, 601 N. Broadway, Baltimore 5, Maryland
Res: 7700 Rider Hill Road, Ruxton 4, Maryland

Dr. Baxter A. Smith (Elaine) (1960) 305 Medical Arts Building, Minneapolis 2, Minnesota
Res: 4603 Edina Boulevard, Minneapolis 24, Minn.

Dr. Donald R. Smith (Eleanor) (1960) University of California Medical Center, 384 Post Street, San Francisco 8, California
Res: 2075 Ninth Ave., San Francisco 22, California

Dr. Harry M. Spence (Lois) (1955) 4105 Live Oak Street, Dallas 1, Texas
Res: 4533 Lorraine, Dallas 5, Texas

Dr. Howard I. Suby (Robin) (1950) 262 Beacon Street, Boston, Mass.
Res: 144 Adams Street, Milton 87, Massachusetts

Dr. John A. Taylor (Elizabeth) (1943) 2 East 54th Street, New York 22, N. Y.
Res: Sigma Place, New York 71, N. Y.

Dr. Gershom J. Thompson (Maxine) (1946) 200 First Street, S. W., Rochester, Minn.
Res: 801 - 12th Avenue, S. W., Rochester, Minn.

Dr. Charles A. W. Uhle (Janet "Jay") (1955) 404 Lankenau Hospital Medical Building, Philadelphia 31, Pa.
Res: Sandy Run Farm, Whitemarsh, Pa.

Dr. William L. Valk (Mary) (1953) University of Kansas Medical Center, Kansas City 12, Kansas
Res: 5401 West 81st Street, Prairie Village, Kansas

Dr. Cornelius Vermeulen (Ruth) (1956) University of Chicago Clinics, 950 East 59th Street, Chicago, Illinois
Res: 1270 Oakmont, Flossmoor, Illinois

Dr. John B. Wear (Laurie) (1937) 1 S. Pinckney Street, Room 616, Madison 3, Wisconsin
Res: 69 Fuller Drive, Madison, Wisconsin

Dr. Henry M. Weyrauch (Helen) (1952) 2201 Webster Street, San Francisco 15, Calif.
Res: 28 Presidio Terrace, San Francisco, Calif.

Dr. Willet F. Whitmore, Jr. (Betsy) (1959) 444 East 68th Street, New York 21, N. Y.
Res: 2 South Drive, Plandome, N. Y.

Dr. William Niles Wishard, Jr. (Carolyn) (1939) 1711 N. Capitol Avenue, Indianapolis 7, Indiana
Res: 5720 N. Pennsylvania Street, Indianapolis 20, Ind.

INACTIVE MEMBERS

Dr. Montague Boyd (Margaret) (1921) 1938 Peachtree Road, Atlanta 9, Georgia
Res: 2560 Habersham Road, N. W., Atlanta 5, Georgia

Dr. Arthur B. Cecil (1921) 1136 West 6th Street, Los Angeles, Calif.

Dr. Edwin Davis (Dorothy) (1922) 800 Doctors Bldg., Omaha, Nebraska
Res: 409 South 38th Avenue, Omaha, Nebraska

Dr. B. H. Hager (Marguerite) (1930)
Res: Willow Creek Ranch, Montague, California

---

* Died May 23, 1961.

Dr. Leon Herman (Leonora) (1933)
Res: 1500 S. W. 4th Street, Ft. Lauderdale, Florida
Dr. C. P. Howze (Hannah) (1934)
Res: 919 Rugby Road, Charlottesville, Virginia
Dr. Thomas F. Laurie (Edith) (1922)
Res: 713 Westcott Street, Syracuse, New York
Dr. George R. Livermore (1922) 1867 Foster Avenue, Memphis, Tennessee
Dr. James C. McClelland (1934) 170 St. George Street, Toronto, Ontario, Canada
Dr. Henry O. Mertz (Ida) (1930)
Res: R. R. No. 1, Nokomis, Florida
Dr. Arthur H. Paine (1922) 2369 Browncroft Blvd., Rochester 10, N. Y.
Dr. Emerson C. Smith (1941) 1390 Sherbrook Street, W., Montreal, Quebec, Canada

DECEASED MEMBERS—1960–1961

Dr. John H. Cunningham (1906) 53 Seaver Street, Brookline, Massachusetts
Dr. William E. Stevens (Emma) (1916)
Res: 2655 Filbert Street, San Francisco 23, Calif.

CONTENTS

OBITUARIES
John Henry Cunningham 2
William E. Stevens 4
Dissemination of Bladder Neoplasms by Endoscopic Electroresection. *H. M. Weyrauch and J. H. Crossfield* 6
Urethral Occurrence of Bladder Carcinoma Following Cystectomy. *J. J. Cordonnier and H. J. Spjut* 13
Relation of Liver Neoplasms to Bladder Tumors Produced by a-Acetylaminofluorene. *J. H. McDonald, R. Oyasu and G. M. Hass* 19
Supervoltage Cobalt-60 Treatment of Bladder Cancer: Palliation or Cure? *L. M. Liegner and J. A. Taylor with Assistance of N. J. Michaud* 29

Discussion

Pararenal Pseudocysts: Report of 4 Cases. *C. L. Sauls and R. M. Nesbit* 44
Multilocular Cyst of Kidney. *T. E. Gibson* 53

Discussion

Progress in Urodynamics. *D. M. Davis with Collaboration of P. Zimskind* 60
Results of Various Procedures Used for Correction of Congenital Ureteropelvic Obstruction. *C. L. Prince and P. L. Scardino* 66

Discussion

Bladder Calculi Formed Around Retained Fragments of Ruptured Foley Catheter Balloons. *R. Chute* 71
Factors Influencing Mortality and Morbidity of Transurethral Prostatectomy: A Study of 2,015 Cases. *H. L. Holtgrewe and W. L. Valk* 75
Transrectal Biopsy to Detect Prostatic Carcinoma: A Review and Report of 203 Cases. *J. L. Emmett, K. W. Barber, Jr. and R. J. Jackman* 85

Discussion

Percutaneous Aspiration of Selected Expanding Renal Lesions. *J. H. DeWeerd* 104

Discussion

Psychosomatic "Cystitis." *D. R. Smith* 113

Discussion

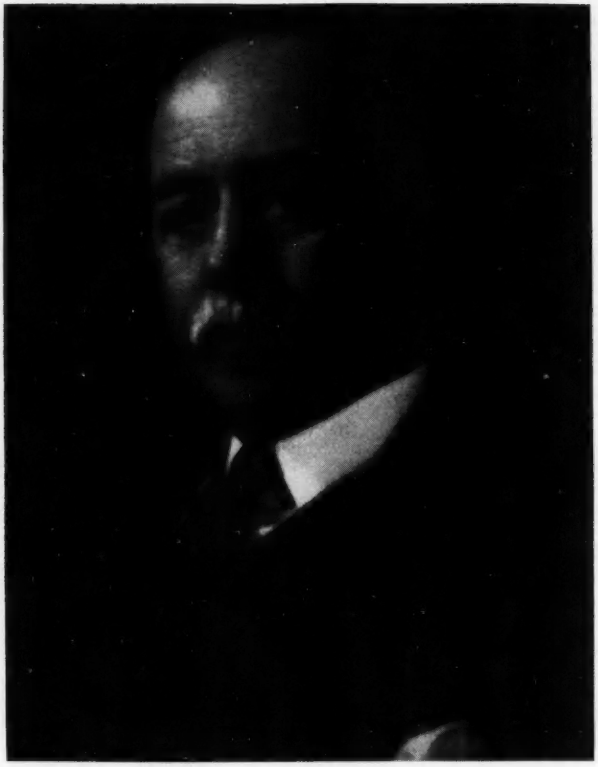
Non-Obstructive Vesicoureteral Regurgitation. *R. A. Garrett, R. K. Rhamy and J. R. Carr* 120
Atrophic Pyelonephritis from Ureteral Reflux without Obstructive Signs ("Reflux Pyelonephritis"). *F. Hinman, Jr. and J. A. Hutch* 125
Importance of Urethral Valves as a Cause of Vesical Neck Obstruction in Children. *K. Waterhouse and F. C. Hamm* 138
Urethral Strictures in Male Children. *G. W. Leadbetter, Jr. and W. F. Leadbetter* 146
Genesis of Benign Polyps in Prostatic Urethra. *R. M. Nesbit* 153
Scrotal and Penile Lymphedema. *G. J. Bulkley* 156

Discussion

Three Atypical Chromatin Positive Male Patients. *R. G. Bunge and J. T. Bradbury* 167
Renal Leukoplakia: Observations of Behavior. *B. A. Smith, Jr., E. A. Webb and W. E. Price* 175
Technical Advances in Prevention of Urinary Tract Infection. *R. E. Desautels, C. W. Walter, R. C. Graves and J. H. Harrison* 184
Changes in Bacterial Enzyme Patterns, Drug Susceptibility and Chemotherapy Through Enzyme Blocking Agents. *H. Seneca, J. K. Lattimer, H. H. Zinsser, J. T. Donovan, P. Peer and P. H. Stuart* 188

Discussion

Investigations on Urolithiasis. II. Studies on Oxalate. *P. F. de Albuquerque and M. Tuma* 196



JOHN HENRY CUNNINGHAM
1878–1960

John Henry Cunningham, in his day one of urology's "greats," died on July 30, 1960, in his eighty-third year. Born in a suburb of Boston, he attended Harvard College and then the Harvard Medical School, graduating in 1902.

In 1908, as junior author, he helped Dr. Francis Watson (who was president of this Association in 1896), to write DISEASES AND SURGERY OF THE GENITO-URINARY SYSTEM. This large two-volume work, nicely printed and with beautiful drawings, many in color, immediately became the leading American book on urology, a position it held for 18 years, until the publication of Hugh Young and David Davis's celebrated YOUNG'S PRACTICE OF UROLOGY in 1926.

Dr. Cunningham's co-authorship of this work, at the age of only 30, plus his ability and his winning personality gained him renown and a large practice at an unusually early age. He wrote numerous articles on urological subjects, and for more than 20 years was editor of the YEARBOOK OF UROLOGY. Within the month the editor of a new volume entitled CLASSIC DESCRIPTIONS IN DIAGNOSTIC ROENTGENOLOGY asked permission to republish a paper by Dr. Cunningham entitled "The Diagnosis of Stricture of the Urethra by the Roentgen Rays" which was printed in the transactions of this Association in 1910, 51 years ago. For many years he was associate in genito-urinary surgery at the Harvard Graduate School of Medicine. He was elected a member of this Association in 1906, and was its president in 1921. He was a member of many societies and clubs, both medical and non-medical. The hos-

pitals with which he was chiefly identified were the Boston City Hospital, where he received his training; and its branch for chronic patients, the Long Island Hospital, of which he was the surgeon-in-chief for a long time.

Dr. Cunningham was so situated financially that he did not have to devote his entire time to medicine, and this allowed his great love for the outdoors to play a more prominent part in his life than is the case with most distinguished practising surgeons. At his summer home on Cape Cod he sailed a great deal. He was fond of hunting both waterfowl and upland game birds, and took many hunting trips. Perhaps his favorite pastime was fishing in either salt or fresh water, much of this being done in the Cape Cod region. Annually for many years in the late winter when the New England climate was, as he said, "in its most fickle mood," he would go with a friend or two, often with Thomas Barbour, the naturalist, to the Caribbean or to Central America, where he would enjoy the beauty of the tropical foliage, and study the monkeys, birds, snakes and butterflies. On such occasions he never failed to do some fishing in the tropical waters of the Atlantic or Pacific.

So far this sketch has failed to mention what was probably most memorable about Jack, as he was affectionately known by his many friends. This was his very great personal charm and his genius for friendship. His nature was warm and friendly, relaxed, cheerful and humorous, but assured and shrewd. He always knew a good story, and was a most delightful companion. Therefore, it is not surprising that he had a host of admiring friends, many of whom were in this Association.

Dr. Cunningham was a bachelor until he was 36, but then had a very happy married life and reared three sons of whom he was very proud. His wife, who survives him, has been distinguished for her outstanding contributions to horticulture, and has received medals from the Massachusetts Horticultural Society and the Garden Club of America.

In the author's opinion, Dr. Cunningham's was the ideal well-rounded life. He worked hard and made worthwhile contributions to urology, and yet was able to have time to devote to his family and to his friends and to the outdoor pursuits of which he was so fond. And all this was done in the aura of his friendly and sensible personality.

RICHARD CHUTE

WILLIAM E. STEVENS

William E. Stevens was born in San Francisco, July 6, 1877; died February 3, 1961 at the venerable age of 84. He received his medical degree from the University of California in 1899. He interned at French Hospital in 1899, and was an extern at San Francisco County Hospital in 1900–1901. He married Emma M. Fortmann in 1901. He was emergency surgeon of San Francisco Emergency Hospitals 1902–1906; was in general practice from 1899–1910, paying special attention to urology 1910–1915, practice limited to urology since 1915; assistant in urology at Franklin Hospital from 1910–1916; assistant in urology at San Francisco Polyclinic, 1912–1918; chief of female urology, 1915–1947; chief of male urology, 1918–1947; chief of urology, Mount Zion Hospital, 1917–1923; visiting urologist, San Francisco County Hospital, 1915–1937; associate clinical professor and senior consultant, Division of Female Urology (Department of Gynecology and Obstetrics) Stanford University, 1923–1942; emeritus associate clinical professor, 1942–1961.

A former director and first vice-president of the San Francisco Medical Society, he was elected an honorary member in 1952; California Medical Association, 1902 (life member, 1948); American Medical Association, 1902; Northern California Urological Society, 1950; American College of Surgeons, 1919; life member, American Medical Association of Vienna, 1924; American Urological Association, 1913; diplomate of American Board of Urology (founders' group), 1935; Western Section, American Urological Association (a charter member and past president), 1930; American Association of Genito Urinary Surgeons, 1930; International Society of Urology, 1952.

LL.D., San Francisco Polyclinic and Postgraduate College, 1942; Sons of the American Revolution; Nu Sigma Nu; Republican; Prot-

estant; Major, U. S. Army Reserve Corps, 1927–1941, then transferred to inactive list.

Dr. Stevens retired from practice in 1950; he is survived by his widow and two children, Francis F. Stevens and Stella Stevens Peschau.

Those of us who had the privilege of knowing Dr. Stevens will always remember him with deep affection and respect. He was the epitome of kindly dignity, always sympathetic and considerate with his patients. He was a man whose character, integrity, and ethical conduct were above reproach. He was a pioneer in female urology in the West. His greatest claim to fame probably rests on his numerous publications on the female urethra as a source of symptoms. He did a great service in drawing the attention of the profession to this much neglected structure. (I am indebted to Dr. Miley B. Wesson for the biographical data cited.)

THOMAS E. GIBSON

DISSEMINATION OF BLADDER NEOPLASMS BY ENDOSCOPIC ELECTRORESECTION

HENRY M. WEYRAUCH AND JOHN H. CROSSFIELD

From the Presbyterian Hospital and Medical Center, San Francisco 15, Cal.

Certain features of cancer of the bladder render it a favorable neoplasm for treatment. With hematuria as an early symptom and accessibility to diagnosis by cystoscopic means, a high proportion of cases come to early recognition. As with all malignant neoplasms, definitive therapy is directed to its elimination before dissemination precludes the possibility of cure. To improve the rate of cure many channels have been explored, including various open operations, electroresection, radiation and chemotherapy.

In the development of methods of therapy one area has been neglected: prevention of the spread of neoplasm during operative procedures. Spread of cancer cells in operative wounds was first investigated by Ryall in 1907,[1, 2] but not until recent years have the dangers been adequately recognized. By initiating a concerted approach, Warren Cole opened new horizons of treatment.

In contrast to recognition of this danger at open operation, it is common belief that endoscopic resection is harmless. The purpose of this paper is to discuss the dangers of spreading bladder neoplasms by transurethral electroresection and to present measures to minimize the hazards.

Although the routes of dissemination are similar to those at open operation, the practical problems are quite different.

POSSIBLE ROUTES OF DISSEMINATION DURING ENDOSCOPIC ELECTRORESECTION

1) *By implantation.* There is both clinical and experimental proof that neoplastic cells develop satellite implants. After resection of bladder tumors, cells germinate upon denuded areas of the bladder and prostatic fossa.[3-5] In experiments on dogs, McDonald successfully transplanted carcinoma tissue to the intact mucosa of the isolated bladder pouch.[6] Tumor cells isolated from the urine have been viable and therefore might be capable of producing new implants.[7, 8]

2) *Spread into and through tissues of the bladder wall.* During transurethral resection, penetration of the mucosal barrier provides access to the muscularis of the bladder and extravesical tissues. From cystographic studies, Bodner and associates estimated that 70 per cent of patients who undergo transurethral resection of bladder tumors extravasate from 100 to 300 cc fluid outside the bladder during the procedure.[9] Their interest was aroused by a patient who required a pelvic operation immediately after transurethral removal of a small carcinoma of the bladder. Upon opening the abdomen the surgeon discovered over 200 cc fluid in the perivesical tissues. By cystometry these workers demonstrated that extravasation occurs at the terminal phase of bladder filling when intravesical pressure rises precipitously. This evidence is supported by cystographic evidence of extravasation after transurethral prostatectomy.[10]

Recurrence of cancer at the site of the original operation 3 years later indicates how difficult it may be to determine whether reappearance of carcinoma following electroresection represents

[1] Ryall, C.: Cancer infection and cancer recurrence: A danger to avoid in cancer operations. Lancet, **2:** 1311, 1907.

[2] Ryall, C.: The technique of cancer operations with reference to the danger of cancer infection. Brit. Med. J., **2:** 1005, 1908.

[3] Borehem, P.: The surgical spread of cancer in urology. Brit. J. Urol., **28:** 163, 1956.

[4] Hinman, F., Jr.: The recurrence of bladder tumors by surgical implantation. J. Urol., **75:** 695, 1956.

[5] Kiefer, J. H.: Bladder recurrence in the urethra: A warning. J. Urol., **69:** 652, 1953.

[6] McDonald, D.: Clinical implications of transplantability of induced bladder tumors to intact transitional epithelium in dogs. J. Urol., **75:** 690, 1956.

[7] Cobb, J. P., Kiefer, J. H. and Wood, F. H.: Human bladder neoplastic cells in tissue culture. J. Urol., **73:** 1039, 1955.

[8] Feeney, J., Mullenix, R. B., Prentiss, R. J., Martin, P. L. and Slate, T. A.: Cytological studies of urine. J. Urol., **79:** 589, 1958.

[9] Bodner, H., Howard, A. H., Kaplan, J. H. and Ross, S. S.: Cystometry during and cystography after transurethral resection of bladder tumor. J. Surg. Research, **1:** 72, 1961.

[10] Conger, K. and Karafin, L.: A study of irrigating media extravasation during transurethral surgery. J. Urol., **78:** 633, 1957.

new growth or recurrence within the wall or adjacent to the bladder.

3) *Hematogenous spread through circulating blood.* Introduction of irrigation medium into the bloodstream renders endoscopic treatment of bladder tumors particularly vulnerable to this kind of spread. Vessels are divided and irrigating solution is forced into these vessels under pressure. The volume of irrigation medium introduced into the venous system has been reported to be as much as 400 to 3,500 ml. fluid during transurethral prostatectomy. The volume is proportional to the irrigating pressure, the size of vessels opened and the time of exposure.[11-13]

Increased numbers of malignant cells have been identified in the circulating blood during operations on neoplasms in practically every organ in the body, including the bladder.[3, 14-17] From clinical observation we know that the presence of malignant cells in the general circulation does not preclude surgical cure, since many such cells are destroyed. However, the greater the number of cells the poorer the prognosis.[18] In experiments upon mice, neoplastic cells recovered from the circulation have produced tumors in normal animals when reinjected.[19]

[11] Griffin, M., Dobson, L. and Weaver, J. C.: Volume of irrigating fluid transferred during transurethral resection: A study with isotopes. J. Urol., **74:** 646, 1955.

[12] Hagstrom, R. S.: Studies of fluid absorption during transurethral resection of the prostate. J. Urol., **73:** 862, 1955.

[13] Taylor, R. O., Maxson, E. S., Carter, F. H., Bethard, W. F. and Prentiss, R. J.: Volumetric, gravimetric and radioisotopic determination of fluid transfer during transurethral resection of the prostate. J. Urol., **79:** 490, 1958.

[14] Cole, W. H. and associates: Cancer cells in the bloodstream. AMA Arch. Surg., **80:** 639, 1960.

[15] Cole, W. H., McGrew, E. A., Roberts, S. S. and Watne, A. L.: The occurrence of cancer cells in the circulating blood and their response to surgery and chemotherapy. Union Internationalis Contra Cancrum Acta, **16:** 790, 1960.

[16] Jonasson, O., Long, L., Roberts, S., McGrew, E. and McDonald, J.: Cancer cells in circulating blood during operative management of genitourinary tumors. J. Urol., **85:** 1, 1961.

[17] Moore, G., Sandberg, A. and Schubarg, J.: Clinical and experimental observation of the occurrence and fate of tumor cells in the blood stream. Ann. Surg., **146:** 580, 1957.

[18] Roberts, S. S., Watne, A. L., McGrath, R. G., McGrew, E. A. and Cole, W. H.: The response of cancer cells in the circulating blood to surgical stress and chemotherapy. Surg. Forum, **9:** 595, 1958.

[19] Jonasson, O.: The viability of circulating cancer cells in experimental cancer. Surg. Forum, **9:** 577, 1958.

4) *By way of the lymphatics.* Division of lymphatics during transurethral resection opens a pathway for metastasis to lymph nodes.

PREVENTIVE MEASURES

With knowledge concerning the ways that neoplastic cells may be disseminated during endoscopic electroresection, we can formulate measures to minimize these hazards. Rules of technique may be grouped into four categories:

1) *Avoid damage to mucosal surfaces.* Although there is danger of implanting neoplastic cells on normal mucosa, perforation of the mucosal barrier enhances the danger of dissemination by opening tissue spaces, blood vessels and lymphatics. Measures to avoid accidental trauma to the mucosa will be discussed before taking up the technique of resection which encompasses a preconceived plan of perforating the mucosal barrier.

Translated into the practical steps of the operation, care is exercised in the following manner:

Use a cystoscopic instrument of the smallest caliber adequate to execute the indicated procedure.

If possible, perform the entire procedure with one instrument.

Copiously lubricate the urethra before inserting the instrument. Inject a sufficient quantity of water-soluble lubricant to distend the entire channel.

Lubricate the instrument with oil before insertion.

Be certain that the cystoscopic sheath has no sharp edges and that the obturator is well seated, not only during introduction but also withdrawal.

Avoid forceful suction in evacuating the bladder to prevent abrasion of the vesical mucosa.

In addition, in resecting bladder tumors do not perform ancillary procedures, such as prostatectomy, which denude additional areas of urothelium.

2) *Minimize release of neoplastic cells.* This applies to preventing release of cells into the cavity of the bladder, the wall of the bladder and surrounding tissue planes. The first step is to attack the pedicle and/or the periphery first, as in ligating the vascular pedicle of the kidney before manipulation of a renal carcinoma. Various techniques have been advocated.

The simplest one of widest application is to

outline the base of the tumor by coagulation and to continue resecting from the periphery to the center of the tumor. Whereas tissue should not be coagulated if the lesion is benign, in bladder tumors coagulation is indicated to seal off tissue spaces, blood vessels and lymphatics. For resecting tumors a blended current is desirable since it coagulates as it cuts.[20]

A technique advocated by Bodner is the pull-off technique, grasping and fulgurating the base of the tumor with specially designed forceps.[21] This technique is applicable only to pedunculated tumors.

Although sealing the base of a tumor is a safeguard, it does not provide an impenetrable barrier. Additional precautions are required to minimize the hazard created by electrosurgical attack. It is important to avoid excessive intravesical pressure, which will lead to extravasation of fluid and possible dissemination of tumor cells. Do not elevate the level of the fluid reservoir more than 18 inches above the bladder; use a safety device to warn when the intravesical pressure rises to a danger point.

3) *Destroy remaining viable neoplastic cells.* Even if the outlined technical precautions are taken, some viable tumor cells will be released. Removal and destruction of remaining cells seem to constitute the weakest link in our chain of precautionary measures, largely because of fragmentary knowledge concerning the use of cytotoxic agents. We know little concerning the effectiveness, local tolerance and systemic effects of drugs capable of destroying tumor cells. Most available data have been derived from animal experiments in which various agents have been tested in wounds[22] and in the peritoneal cavity[23] following inoculation with tumor cells.

There is need to supplement these observations with studies which will determine the most effective preparations which will produce no harmful local or systemic effect. Ideally we seek a cytotoxic solution which may be used as an irrigation medium. Acting continuously throughout the procedure, it would minimize the risk of local implantation and of dissemination.

TABLE 1. *Irrigation wounds inoculated with 256 Walker carcinosarcoma cells one hour previously**

Solution	No. Rats	% Takes
Control, no irrigation	86	89%
Normal saline	32	100%
Distilled water	10	100%
Phenol 0.1%	36	86%
Mercury bichloride 1:1000	30	66%
Ethyl alcohol 95%	7	57%
Nitrogen mustard 1 mg. %	30	3%
Clorpactin 2%	38	5%

* Taken from Collier, Ey, McDonald and Cole: AMA Arch. Surg., **78:** 528, 1959.

Hinman[4] advocated instillation of 100 ml. solution of 1 to 500 phenol to be left in the bladder for one hour and then released. From experience in treating tuberculous cystitis we know that this is a safe procedure. We have no knowledge, however, concerning the toxicity of this solution were it to be used as an irrigation medium. In wound irrigation experiments[22] a less concentrated solution of phenol (1 to 1,000 solution) exerted limited cytotoxic activity in reducing the incidence of tumor takes to 86 per cent (table 1).

Clorpactin XCB was more cytotoxic in these experiments. By use of a 2 per cent solution there were only 5 per cent takes, in contrast to 86 per cent with phenol 1 to 1,000. Unfortunately, a 0.2 per cent solution of clorpactin is the most concentrated that is tolerated by the bladder, in contrast to the 2 per cent used in the wound experiments. Therefore, proof is lacking of the suitability of this drug.

Podophyllin may have application as an instillation to destroy free tumor cells. This drug has demonstrated some effectiveness in the local treatment of bladder tumors.[24, 25]

In seeking a cytotoxic agent suitable for use as

[20] Weyrauch, H. M., Bassett, J. B. and Burger, M. M.: Practical considerations in the use of high frequency currents for transurethral prostatectomy. J. Urol., **61:** 371, 1949.

[21] Bodner, H.: Utility forceps for resectoscope. J. Urol., **83:** 209, 1960.

[22] Collier, R. G., Ey, R. C., McDonald, G. O. and Cole, W. H.: Wound irrigation to prevent local recurrence of cancer. AMA Arch. Surg., **78:** 528, 1959.

[23] Thomas, C., Weeks, P. and Brown, B.: Control of free tumor cell growth by topical chemotherapeutic agents. Surg. Forum, **9:** 595, 1958.

[24] Bunge, R. G.: Podophyllin in treatment of human adenocarcinoma of bladder. J. Urol., **68:** 375, 1952.

[25] Richardson, E. J.: Use of podophyllin in treatment of papillomatosis of the bladder. J. Urol., **82:** 234, 1959.

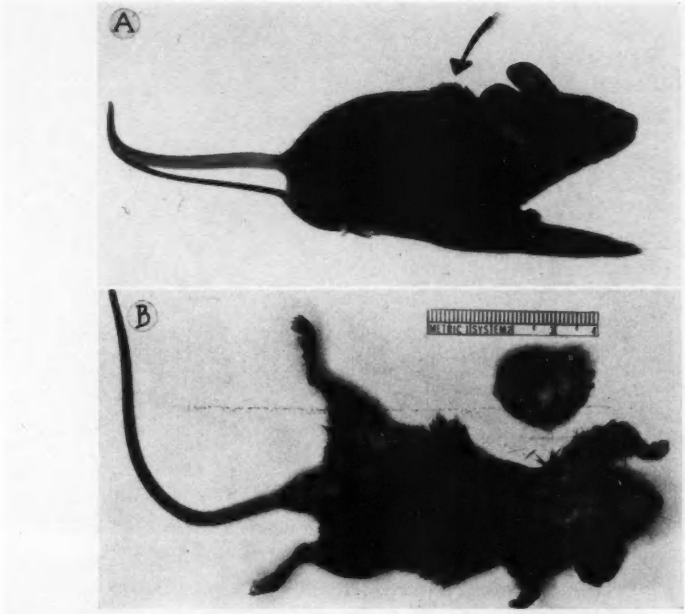


FIG. 1. *A*, arrow points to subcutaneous tumor 2 weeks after transplant to C57 mouse. *B*, tumor dissected from subcutaneous tissues.

an irrigation medium, we have been favorably impressed with the possibility of using phenazine-di-N-oxide (fig. 1). This newly developed carcinostatic drug has demonstrated startling effectiveness in destroying Ehrlich ascites tumor in the peritoneal cavity of mice.[26] More than 90 per cent of tumor-bearing animals treated with 75 mg./kg. of this compound survived 30 days or more and were rendered free of tumor while the average survival of an untreated control group was 13 days. Comparison of phenazine-di-N-oxide with other drugs active against this tumor showed that 6-mercaptopurine, administered intraperitoneally, and N-methylformamide, given orally, extended the mean survival time by 25 to 100 per cent, but all animals died with tumor. Other phenazine compounds, such as the dye Janus green B, have shown activity against transplanted mouse tumor, but only at toxic levels.

Phenazine-di-N-oxide apparently interrupts electron transfer and thus interferes with the respiration of the cell. This compound used as an irrigation medium has been of low toxicity to rats. When injected into the peritoneum in the dose of 75 mg./kg. no changes could be seen in the kidney, adrenal, liver, thymus, lymph node, heart, brain or lungs. When injected into the bladder a saturated solution in tumor dose amounts (75 mg./kg) produced no local change or abnormality of the organs listed, nor did this dose given intravenously to rats produce any changes. However, when the dose was increased to 1200 mg./kg. and given intravenously to rats, all organs showed edema and vascular congestion. Nevertheless all animals survived. Further tests for acute and chronic toxicity will be performed on experimental animals before making any preliminary clinical application of this drug.

One factor which contributes to the low toxicity is that when the drug enters the circulation it rapidly enters the stomach and is excreted in the feces. A saturated solution of 15,000 cc, an amount adequate for irrigation during an extensive bladder resection, contains 750 mg. drug. If it were possible for a patient weighing 70

[26] Furst, A., Clausner, T. and Cutting, W. C.: Phenazine-di-N-oxide as a carcinostatic agent. Nature, **84**: 908, 1959.

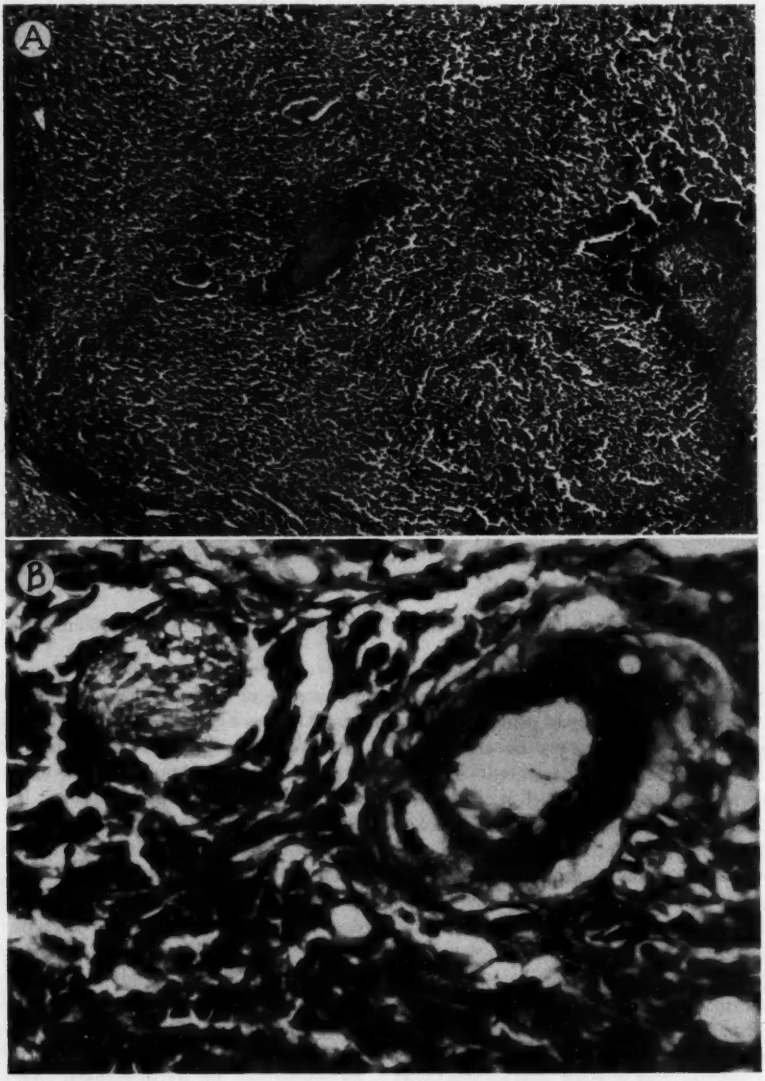


FIG. 2. Microscopic appearance of Lewis bladder tumor. *A*, low power (H & E stain, ×80). *B*, high power (H & E stain, ×120).

kilograms to absorb all this solution (15,000 cc) without drowning in body fluids, the systemic dose would be less than 11 mg./kg. while the effective tumor dose is 75 mg./kg. in rats and mice.

Since phenazine-di-N-oxide is practically insoluble, it is mixed with a suspending material—carboxy methyl cellulose (CMC). A solution of 5 mg. per cent is prepared with 1 per cent CMC. Pending demonstration, neither phenazine-di-N-oxide nor CMC appears to possess electrolytic activity which would interfere with the cutting or fulgurating qualities of electrosurgical currents.

We are testing the cytotoxicity of phenazine-

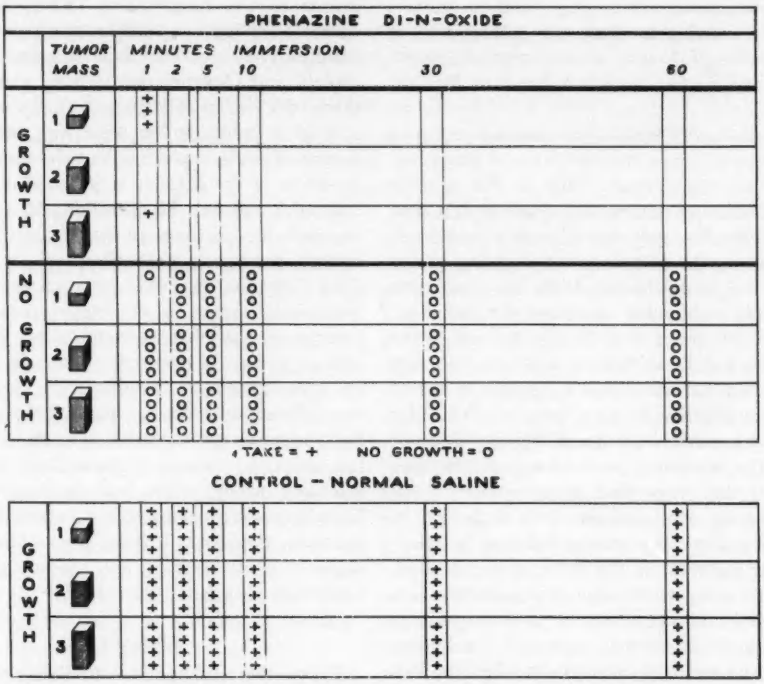


FIG. 3. Results after immersion of tumor tissue of 1 by 1 by 1 mm., 2 by 1 by 1 mm. and 3 by 1 by 1 mm. in saturated solution of phenazine-di-N-oxide for indicated times before subcutaneous transplantation.

di-N-oxide against the Lewis bladder tumor in mice. This tumor was induced by wrapping the mucosa from the bladder of the mouse about crystals of 20-methyl cholanthrene and implanting the mass subcutaneously.[27] The resulting tumor is well established and can be transplanted from one generation to the next on a predictable basis. It produces 100 per cent metastasis to the lungs within 16 to 24 days but not to other organs.[28] The tumor is maintained on a routine 2-week transplant basis, during which time a subcutaneous mass over 2 cm. in diameter develops (fig. 2). Microscopically it is an undifferentiated carcinoma without tendency to form glands or papillary arrangement. The cells are polygonal, containing large oval to round nuclei with coarse chromatin and ill-defined borders.

[27] Hughes, B.: Induction of transplantable bladder carcinoma in inbred strains of mice. J. Urol., **62**: 833, 1949.

[28] Baserga, R. and Saffiatti, U.: Experimental studies on histogenesis of blood borne metastasis. AMA Arch. Path., **59**: 26, 1955.

We have succeeded in maintaining this tumor in Swiss-Webster mice in addition to C57 mice used as hosts by the original investigator. The tumor has retained histologic characteristics identical to those observed in C57 mice.

Upon immersing tumor implants of three sizes in a saturated solution of phenazine-di-N-oxide for different times, and then inoculating them into the subcutaneous tissue of the Swiss-Webster mice the following results were observed (fig. 3). One hundred per cent of the control transplants survived and proliferated. Of those treated with phenazine-di-N-oxide, only four of 30 mice had a successful surviving transplant of the tumor immersed for 1 minute. No viable cells survived immersion for up to two minutes.

We are developing an ascites form of the Lewis bladder tumor. Isolated cells will more closely simulate tumor cells released during resection and will permit injection of a solution containing known numbers of cells into the cavity and wall of the bladder and perivesical tissues. We plan

also to do experiments on dogs. In these animals it will be possible to study the pathogenesis of dissemination following experimental electroresection and to use tumors induced in the test animals.

4) There is more factual information concerning a final precautionary measure to avoid dissemination by electroresection. This is the *systemic administration of cancerocidal drugs* at the time of operation. The rationale of such a program is supported by the demonstration that free cancer cells are frequently liberated into the circulation of patients undergoing operation for malignant tumors,[29] by proof that malignant cells have been destroyed in animals by cancerocidal drugs and by demonstration that cancerocidal agents have been effective in the treatment of bladder cancer. Cole advised the use of nitrogen mustard during the operative period on patients with cancer of the breast and large bowel.[30, 31] Although he has employed this form of therapy in over 136 patients the time of followup is inadequate for appraisal of the value of the method.

We are using triethylene thiophosphoramide (thio-TEPA) at operation to protect patients with bladder carcinoma. Although no known cancerocidal agent is universally effective, this drug has yielded good results in the treatment of some bladder and prostatic carcinomas.[32, 33] Thio-TEPA given shortly after the intravenous administration of S-91 melanoma tumor cells in mice has reduced the number of metastatic lesions in the lung.[34] Thio-TEPA, like other cancerocidal agents, differs qualitatively and quantitatively in its effectiveness against different clinical and experimental tumors, even among those with similar cellular pattern. An advantage is that it produces few toxic side effects. The dosage schedule, depending on weight and general condition of the patient, is 20 to 30 mg. (intravenously) the day of operation; 10 to 15 mg. the first day postoperatively; 10 to 15 mg. the second day postoperatively, making a total dose of 40 to 60 mg. This dosage rarely produces leukopenia except in debilitated patients, yet experience has demonstrated that it should prove effective in destroying free cells liberated at operation.[35] In administering thio-TEPA especial caution must be exercised if the patient has undergone recent radiation or chemotherapy, has extensive osseous metastasis or any other condition which might lead to suppression of hematopoietic elements of bone marrow. During intensive therapy a leukocyte count should be made at least biweekly, and therapy should be postponed if it falls below 4,000.[32]

[29] Morales, F., Bell, M., McDonald, G. O. and Cole, W. H.: The prophylactic treatment of cancer at the time of operation. Ann. Surg., **146:** 588, 1957.

[30] Miazek, R., Economou, S., McDonald, G. O., Slaughter, D. P. and Cole, W. H.: Prophylactic and adjuvant use of nitrogen mustard in surgical treatment of cancer. Ann. Surg., **150:** 745, 1959.

[31] Cole, W. H.: Prophylactic treatment of malignant disease with nitrogen mustard and thio-TEPA. Ann. Surg., **145:** 624, 1957.

[32] Hall, B. E., Willett, F. M. and Hales, D. R.: Observations on effects of alkylating agents in human neoplastic disease. Ann. Int. Med., **52:** 602, 1960.

[33] Weyrauch, H. M. and Nesbet, J. D.: Use of triethylene thio-phosphoramide (thio-TEPA) in treatment of advanced carcinoma of prostate. J. Urol., **81:** 185, 1959.

[34] Kramer, W. M., Eck, R. V. and Smith, R. R.: Prevention of rat lung metastasis with thio-TEPA. Surg., Gynec. & Obst., **106:** 427, 1958.

[35] Hall, B.: Personal communication.

SUMMARY

From the standpoint of dissemination of bladder neoplasms, electroresection may be as hazardous as removal of neoplasms by open operation. In discussing the problems peculiar to this type of surgery we have attempted to present urologic techniques which will reduce the dangers of dissemination and to point the way to new frontiers which should be explored to provide every possible safeguard to patients who undergo this procedure.

ADDITIONAL REFERENCES

Cole, W. H.: Cancer of the colon with reference to prevention of recurrence. J.A.M.A., **155:** 1549, 1954.

Lewis, M. R. and Cole, W. H.: Experimental increase of lung metastasis after operative trauma. AMA Arch. Surg., **77:** 621, 1958.

URETHRAL OCCURRENCE OF BLADDER CARCINOMA FOLLOWING CYSTECTOMY

JUSTIN J. CORDONNIER AND HARLAN J. SPJUT

From Department of Surgery, Section on Urology and Surgical Pathology, Washington University School of Medicine, St. Louis, Mo.

A recent review of male patients in whom cystectomy was performed for carcinoma of the bladder revealed the interesting fact that of a total of 174 cases, seven (4.02 per cent) had recurrent carcinoma in the urethra. In some, the urethral recurrence was followed by lymph node metastases, with an eventual fatal outcome. A single case of recurrence in the female urethra, with spread to the vagina, will also be discussed because of some unusual aspects of the case.

In 1945, Melicow[1] pointed out that in papillary tumors of the renal pelvis, tumors may also be present in the ureter, bladder, or urethra. Zaslow and Priestley,[2] in analyzing primary carcinomas of the male urethra, mentioned that they had eliminated the "few" in which small epitheliomas had developed subsequent to total cystectomy for carcinoma of the bladder.

In 1948, in a discussion of Dukes and Messina's presentation of the pathology of primary carcinoma of the urinary bladder, Millin,[3] Young,[4] and Adams[5] each reported a single case of recurrence of carcinoma in the urethra following cystectomy for cancer of the bladder. Melicow and Hollowell,[6] reported 30 cases of intra-urothelial cancer including five in the urethra and suggested the possibility that precancerous changes in the mucosa were present in various levels of the urothelium and were probably responsible for the recurrences. Included in their report were 3 cases in the prostatic and two in the anterior urethra.

Baird, Bush and Livingstone[7] reported 2 cases of urethral recurrence following cystectomy, and made the suggestion that urethrectomy might be indicated at the time of cystectomy.

Ashworth[8] presented the only statistical analysis available in which the total number of cases involved is given. He reviewed 1307 patients with epithelial tumors of the bladder and found 54 with urethral papillomas (4.1 per cent), a figure strikingly similar to our own recurrence rate. Of these, seven were classified as appearing in the anterior urethra. Of the 7 patients with anterior urethral papillomas, five had a thick growth of papillomas in the posterior urethra as well. The other two had cystectomy and the urethral lesions appeared 2½ years and 1 year later respectively. It was Ashworth's impression that multiple endoscopic procedures may have contributed to the presence of the urethral lesions. He stated that recurrence in the urethra following cystectomy might be treated by fulguration, but suggested that urethrectomy was probably preferable. In 91 per cent of the urethral recurrences, the primary lesion of the bladder was papillary carcinoma.

Boreham[9] stated that it was doubtful that transitional cell carcinoma would spread in the urinary tract unless there was some break in the mucosa. It was his feeling that most urethral lesions were secondary to implantation. He reported 3 cases of tumor in the anterior urethra following cystectomy. The first and second each had recurrence in the urethra approximately 6 months after cystectomy.

Gowing,[10] in 1960, presented an extensive

[1] Melicow, M. M.: Tumors of the urinary drainage tract: Urothelial tumors. J. Urol., **54:** 186–193, 1945.

[2] Zaslow, J. and Priestley, J. T.: Primary carcinoma of the male urethra. J. Urol., **58:** 207–210, 1947.

[3] Millin, T. J.: Discussion. Brit. J. Urol., **21:** 293, 1948.

[4] Young, J. N.: Discussion. Brit. J. Urol., **21:** 293, 1948.

[5] Adams, A. W.: Discussion. Brit. J. Urol., **21:** 294, 1948.

[6] Melicow, M. M. and Hollowell, J. W.: Intra-urothelial cancer: Carcinoma in situ, Bowen's disease of the urinary system: Discussion of thirty cases. J. Urol., **68:** 763–772, 1952.

[7] Baird, S. S., Bush, L. and Livingstone, A. G.: Urethrectomy subsequent to total cystectomy for papillary carcinoma of the bladder: Case reports. J. Urol., **74:** 621–625, 1955.

[8] Ashworth, A.: Papillomatosis of the urethra. Brit. J. Urol., **28:** 3–13, 1956.

[9] Boreham, P.: The surgical spread of cancer in urology. Brit. J. Urol., **28:** 163–175, 1956.

[10] Gowing, N. F. C.: Urethral carcinoma associated with cancer of the bladder. Brit. J. Urol., **32:** 428–438, 1960.

discussion on the probable etiology of urethral recurrence following cystectomy for bladder carcinoma and discussed in detail 3 patients with urethral carcinoma in whom cystectomy had been performed. He made no statement as to the total number of patients involved, so it is impossible to estimate percentage of recurrence from his series. He noted that in all 3 cases the lesions were multiple and seemed to originate from a wide field of surface epithelium. He further observed that distant sections of the urethra showed carcinoma in situ and carcinoma in the ducts of the mucus glands. A review of the male urethra in a series of 33 patients on whom cystectomy had been performed for carcinoma showed carcinoma in situ in 8 per cent, in comparison with none in a control series of 34 male urethras examined post mortem, in patients dying from other causes. He noted that the carcinoma in situ lesions were always patchy with many areas of normal epithelium, and favored the frequency of multicentric in situ changes as the most likely etiology of urethral recurrences.

CASE REPORTS

Case 1. R. S. Cystectomy, prostatovesiculectomy, and ileal loop diversion were performed on October 8, 1957. Microscopic sections from the bladder showed transitional cell carcinoma, grade 3, Jewett A, with additional areas of cystitis cystica and glandularis appearing in the bladder. On June 28, 1960, the patient noticed a brownish urethral discharge, and two roughened areas in the mucosa of the midportion of the penile urethra were found to be the source of bleeding.

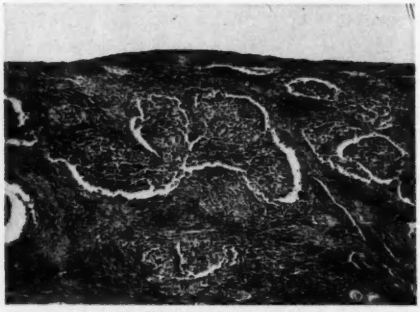


FIG. 1. Case 1. Photomicrograph. Poorly differentiated transitional cell carcinoma in subepithelial connective tissue of urethra. Because of these findings, carcinoma was thought to be either metastatic to urethra or invasive. W.U. Ill. No. 61-327. Hematoxylin-eosin, ×55.

On July 29, a urethrectomy was performed. The lesion was limited to the midportion of the urethra and showed metastatic carcinoma lying in islands beneath the intact mucosa (fig. 1).

Case 2. E. W. Cystectomy, prostatovesiculectomy, and ileal loop diversion were performed on June 26, 1956. Removed tissue showed multiple transitional cell papillary carcinoma grade 2, Jewett A. Numerous areas of squamous metaplasia were noted in the prostate. On May 1, 1957, a bloody urethral discharge appeared and numerous papillary lesions were noted in the penile and bulbous urethra on cystourethroscopy. Biopsy showed transitional cell carcinoma, grade 2. On May 11, a urethrectomy was performed. Scattered along the entire urethra were multiple small separate and concurrent raised lesions, typical small papillomas of the mucosa. At no point was there any invasion of muscle and the proximal line of resection was free of tumor. On July 8, 1960, an abdominal mass was found on biopsy to contain epidermoid carcinoma, from which the patient subsequently died.

Case 3. G. S. The patient underwent cystectomy and prostatovesiculectomy with ileal loop diversion on November 13, 1953, for multiple rapidly recurrent superficial grade 2 carcinoma of the bladder without muscle invasion. On April 19, 1956, urethral bleeding occurred. No mass was palpable rectally or in the urethra. Urethroscopy revealed multiple papillary lesions deep in the urethra and a biopsy showed transitional cell carcinoma, grade 2. The posterior and bulbous urethra was excised, but for some unexplained reason the entire urethra was not removed. Interestingly enough no tumor was found in the excised urethra; apparently the entire lesion had been removed with the resectoscope at the time of biopsy. On September 10, 1957, the patient felt a mass in the right groin and a papillary lesion was noted in the fossa navicularis. Biopsy showed transitional cell carcinoma both in the fossa navicularis and the inguinal lymph node. The outcome was fatal.

Case 4. V. A. On December 11, 1956, cystectomy was performed for transitional cell carcinoma, grade 2, Jewett C. Foci of transitional cells resembling tumor were also noted in the prostate and in the stump of the left ureter. Intravenous urograms prior to surgery failed to visualize the left kidney, and it was impossible to catheterize the ureter because of the extent of

tumor involving the left orifice. Following surgery, a catheter was left indwelling in the ureter and retrograde pyelograms showed transitional cell carcinoma of the left kidney pelvis. Therefore, on December 27, a left nephroureterectomy was performed. On March 13, 1957, the patient noticed a bloody urethral discharge and cystourethroscopy revealed multiple papillary tumors involving the entire urethra to within 3 cm. of the urethral meatus. These tumors were apparently well controlled by multiple fulgurations. However, the patient died on January 29, 1958, of multiple metastases. The multiplicity of the primary lesions and the early presence of urethral lesions suggest thet they were present prior to surgery and were not diagnosed.

Case 4. W. B. The patient underwent cystectomy, prostatovesiculectomy, and ileal loop diversion on October 31, 1957, for multiple recurring transitional cell carcinoma, grade 2, limited to the mucosa. Hyperplasia of epithelium was noted in the prostatic ducts. The patient returned on April 10, 1960, with a bloody urethral discharge. Inspection of the urethra did not reveal a definite lesion but scrapings from the bulbous urethra showed transitional cell carcinoma, grade 1. The rest of the urethra looked perfectly smooth and there was no evidence of tumor. Because the cardiac status was poor, radium was placed in a urethral catheter and applied to the closed end of the urethra. The patient returned on July 8, with further bloody urethral discharge and palpable nodules along the course of the urethra. On July 9, a urethrectomy was performed. Most of the urethra showed no tumor grossly. However, in about the midportion there was a rather large transitional cell carcinoma arising from the urethral mucosa. This tumor was very similar to the primary lesion in the bladder. No tumor was noted in the proximal stump in the radiated area (fig. 2).

Case 5. A. C. On November 30, 1959, cystectomy, prostatovesiculectomy, and ileal loop diversion were performed for transitional cell carcinoma grade 4, Jewett B_2 (fig. 3, *A*). On January 4, 1960, the patient complained of pain in the perineum, and penile shaft and tender swollen areas were present along the course of the urethra. Tissue removed from the urethra by transurethral resection showed undifferentiated carcinoma (fig. 3, *B*). Rectal palpation disclosed a recurrence in the prostatic fossa. A mass was seen on urethroscopy at the penoscrotal junction of the urethra. Becase of the extent of the carcinoma, the patient was treated with radiation therapy. He died February 26, of multiple carcinomatosis. This case probably presents direct metastatic spread of an extensive carcinoma.

Case 6. J. K. On April 5, 1958, cystectomy, prostatovesiculectomy, and ileal loop diversion were performed. The bladder showed a superficial transitional cell carcinoma, grade 3 or 4, without muscle invasion. The prostatic urethra showed carcinoma in situ and one prostatic gland appeared to have been invaded by carcinoma. Both of these areas were proximal to the line of exci-

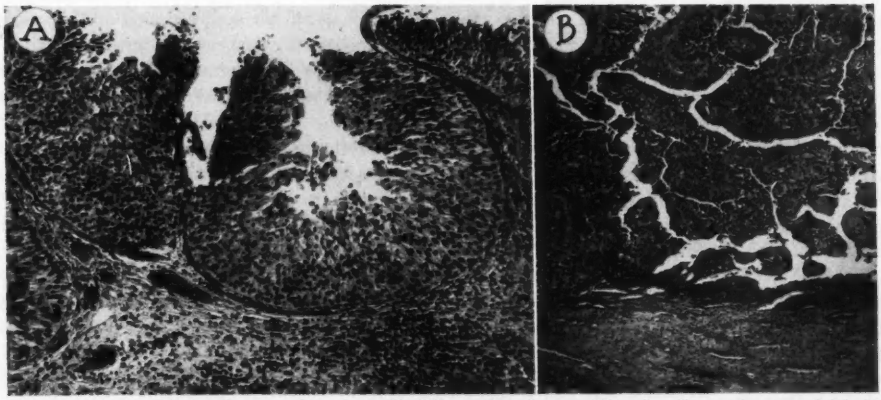


FIG. 2. Case 4. Photomicrographs. *A*, well differentiated transitional cell carcinoma of bladder. Muscle invasion was not present. W.U. Ill. No. 61-330. Hematoxylin-eosin, ×117. *B*, note well differentiated papillary transitional cell carcinoma of urethra. It appeared 30 months after cystectomy. W.U. Ill. No. 61-329. Hematoxylin-eosin, ×40.

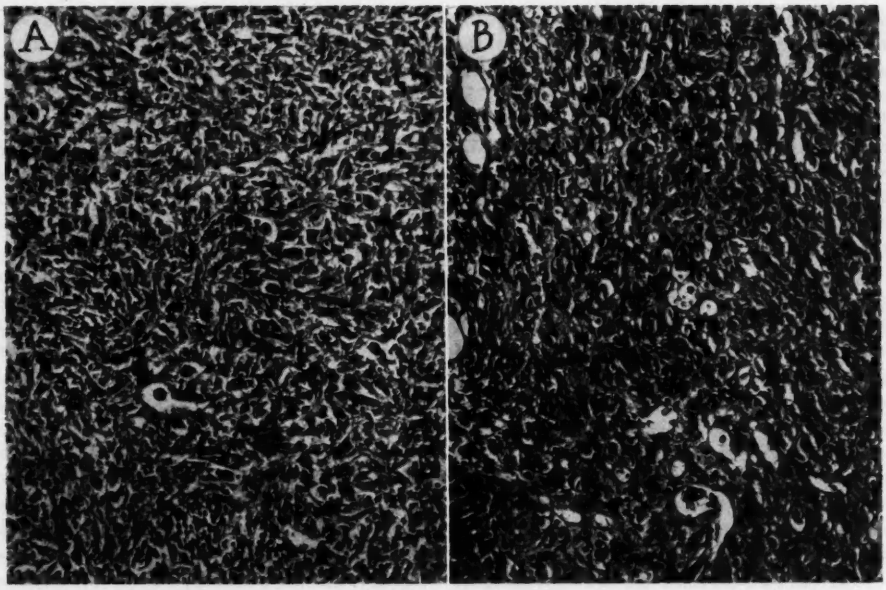


FIG. 3. Case 5. Photomicrographs. *A*, undifferentiated carcinoma of bladder. W.U. Ill. No. 61-334. Hematoxylin-eosin, ×130. *B*, carcinoma of urethra is histologically similar to that of bladder. W.U. Ill. No. 61-333. Hematoxylin-eosin, ×130.

sion. On May 21, 1960, the patient noticed a bloody urethral discharge. Rectal examination disclosed a mass in the prostatic fossa. Urethroscopic examination and scrapings from the urethra showed transitional cell carcinoma. Transrectal biopsy of the mass in the prostatic fossa also revealed carcinoma. The patient was given supervoltage radiation therapy but the carcinoma progressed rapidly to include the entire penis and he died of multiple metastases on February 4, 1961. In this case certainly a substantial amount of benefit might have been obtained by total urethrectomy at the time of surgery. We should have been suspicious of the pathological findings of carcinoma in situ in the prostatic urethra. In all probability similar lesions were also present but unrecognized in the remainder of the urethra.

Case 7. P. W. Since it is our custom to perform total urethrectomy in all female patients, carcinoma of the urethra has not developed with the exception of this patient. She was seen for the first time on April 6, 1959 because of painless hematuria. Examination revealed right hydronephrosis and hydroureter and carcinoma in the midportion of the ureter. On April 10, nephroureterectomy was performed including a substantial cuff of bladder. The ureter was quite friable and there was some spillage during the surgery. The pathological report showed transitional cell carcinoma, grade 1, without muscle invasion. Because of the question of spillage, the patient received supervoltage cobalt radiation to the bladder and the right lower quadrant of the abdomen (4200 r.u. over a period of 37 days). On September 16, 1959, she returned because of recurrence of hematuria and was found to have a papillary tumor extending over the right lateral wall of the bladder. This lesion was resected transurethrally and was reported as transitional cell carcinoma, grade 1 superficial. Tumors continued to reappear in various areas of the bladder with some increase in degree of malignancy (fig. 4, *A*). Therefore, after multiple endoscopic treatments, on June 15, 1960, cystectomy and panhysterectomy were performed with urinary diversion into an ileal segment. Abdominal exploration revealed no evidence of either local spread or metastases. The entire operation was extremely difficult from a technical standpoint because of prior radiation. Therefore, more than the usual amount of manipulation was

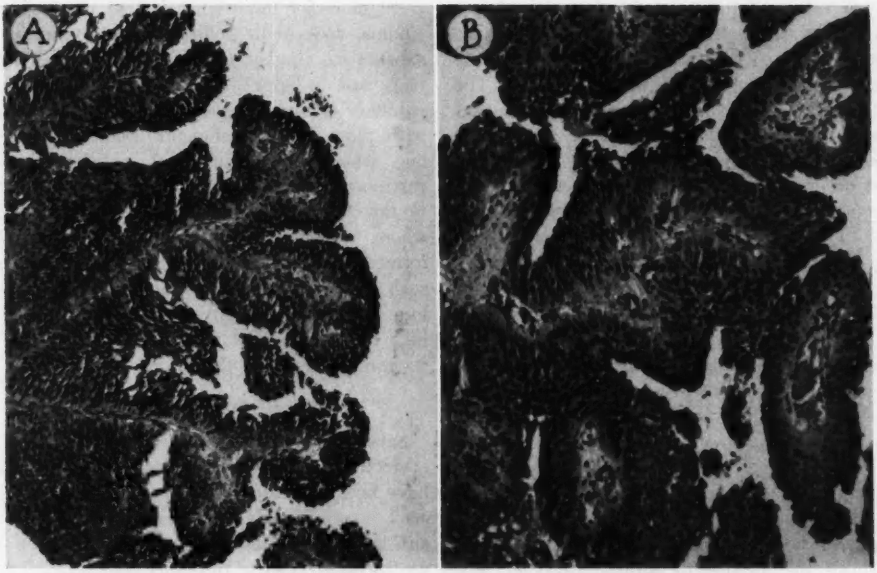


FIG. 4. Case 7. Photomicrographs. *A*, well differentiated papillary transitional cell carcinoma of bladder. W.U. Ill. No. 61-331. Hematoxylin-eosin, ×95. *B*, papillary carcinoma of urethral meatus. Lesion is similar to that of bladder. W.U. Ill. No. 61-332. Hematoxylin-eosin, ×130.

employed and it is quite possible that the entire urethra was not removed. Convalescence was uneventful and there was no further trouble until September 23, when she complained of vaginal bleeding. An area of tumor was present at the urethral meatus and multiple papillary lesions were scattered over the entire vagina. Microscopic sections of these removed areas showed transitional cell carcinoma, grade 2 (fig. 4, *B*). Because of the multiplicity of the lesions, the patient was anesthetized and the multiple areas fulgurated. To date this seems to be effective as no new lesions have appeared.

The clinical course suggests that both the vesical and vaginal tumors were implants secondary to manipulation.

TABLE 1. *Summary of cases*

Case	Grade Of Bladder Tumor	Grade Of Urethral Tumor	Interval between Cystectomy and Urethral Carcinoma
R.S.	3	3	33 mos.
E.W.	2	3	11 mos.
G.S.	2 with ca. in situ	2 & 3	29 mos.
V.A.	2	2	4 mos.
W.B.	2	2	30 mos.
A.C.	4	4	1 mo.
J.K.	4 with ca. in situ	4 with ca. in situ	25 mos.
P.W.	2	2	3 mos.

DISCUSSION

Since five of the 8 patients in whom urethral recurrence appeared (table 1) died rather promptly, this must be considered a serious complication. The presenting sign of urethral recurrence has invariably been that of bloody urethral discharge.

Histologically the urethral carcinomas were similar to those of the bladder, both in configuration and grade. The urethral carcinoma appeared from 1 month to 2 years 9 months after cystectomy. Four appeared after 2 years; the other four were manifest in less than one year. The time of occurrence of the urethral lesion did not seem to be related to grade of malignancy as two of the four lesions appearing after 2 years were grades 3 and 4; the others were grade 2.

From the histologic considerations it is difficult

to be certain of the origin of the urethral carcinomas, i.e. whether primary or metastatic. Except for two of the cases (R.S. and A.C.) the urethral lesions appeared to be primary. The two exceptions may have been metastases in that intact urethral epithelium covered the tumor. Thus it seems possible that neoplastic transformation occurred in the urethral epithelium in the absence of the urinary stream. If present before interruption of the urinary outflow, thus at least one could say that the lesions progressed, sometimes rapidly, in the absence of urine flow.

It has been suggested that three primary methods of spread may occur: 1) lymphatic, 2) seeding on the epithelial surface, and 3) the presence of multicentric areas of carcinoma in situ in the urethral mucosa which subsequently develop into malignant tumors. Review of the various pathologic sections in our series would suggest that any one or more of these theories might be applicable in each individual case and it would be mere speculation to attempt to establish the method of spread. However, the point of major importance is that urethral carcinoma does occur following cystectomy in a substantial number of patients. Although it is more apt to appear in patients with multiple papillary low grade lesions, it may occur as well with more highly malignant lesions; therefore, one cannot predict in which patient urethral carcinoma is most likely to develop. Should total urethrectomy be included in all male patients on whom cystectomy and prostatectomy are performed for carcinoma of the bladder? Although such a step would add about an hour to an already long and difficult operative procedure, the fairly high rate of urethral recurrence would seem to warrant inclusion of this added step.

SUMMARY

Seven cases of urethral recurrence following cystectomy for carcinoma of the urinary bladder have been presented. This represents a 4.02 per cent recurrence rate, and is considered to be of sufficient importance to warrant inclusion of urethrectomy at the time of cystectomy.

THE RELATION OF LIVER NEOPLASMS TO BLADDER TUMORS PRODUCED BY 2-ACETYLAMINOFLUORENE

JAMES H. McDONALD, RYOICHI OYASU AND GEORGE M. HASS

From the Department of Surgery, Division of Urology, of the University of Illinois College of Medicine and the Division of Pathology of the Presbyterian-St. Luke's Hospital of Chicago, Ill.

Much additional evidence is essential if the current concept of the urine transport of carcinogenic substances as an etiologic factor in spontaneous bladder carcinoma is to be accepted. Outstanding advances have been made in the evaluation of occupational bladder cancer, but much more must be added to the present accomplishments in the development and study of experimentally-induced bladder tumors in animals.[1-10]

Investigations of bladder tumors in animals were greatly stimulated following the 1941 report by Wilson, De Eds and Cox[11] on the carcinogenic effect on the urinary bladder of 2-acetylaminofluorene (2-AAF).* Subsequent work further revealed the potency and the wide range of species and tissues affected by this agent.[12, 13] However, it remained for Dunning and Curtis in 1953 to show a marked increase in 2-AAF-induced bladder tumors in the rat by adding an excess of DL-tryptophan or indole to the diet.[14, 15] The role of these substances in enhancing the development of bladder tumors by 2-AAF remains unclear, though it is known that neither tryptophan nor indole produces any demonstrable changes in the bladder. Tryptophan is an essential amino acid in the human, with indole being a product of the normal metabolism of tryptophan. Demonstration of the role of these compounds in the development of bladder tumors in animals may lead to a more explicit direction in developing the urogenous theory of spontaneous bladder carcinoma in the human.

This study deals primarily with the histopathology of 2-AAF-induced bladder tumors in the rat with preliminary inquiry into the mechanism of action of indole as a co-carcinogen.

MATERIALS AND METHODS

Two hundred and forty-six Charles River W (Wistar) male rats weighing 122 to 139 gm. were

This study was supported by the Public Health Service (Grant No. C-5378).

[1] Bonser, G. M., Clayson, D. B., Jull, J. W. and Pyrah, L. N.: The carcinogenic activity of 2-naphthylamine. Brit. J. Cancer, **10:** 533–538, 1956.

[2] Bonser, G. M.: Epithelial tumours of the bladder in dogs induced by pure beta-naphthylamine. J. Path. & Bact., **55:** 1–6, 1943.

[3] Bonser, G. M., Clayson, D. B., Jull, J. W. and Pyrah, L. N.: The carcinogenic properties of 2-amino-1-naphthol hydrochloride and its parent amine 2-naphthylamine. Brit. J. Cancer, **6:** 412–424, 1952.

[4] Boyland, E. and Manson, D.: The metabolites of 2-naphthylamine produced by rats and rabbits. Biochem. J. Proc., 2, **60:** ii–iii, 1955.

[5] Boyland, E., Harris, J. and Horning, E. S.: The induction of carcinoma of the bladder in rats with acetamidofluorene. Brit. J. Cancer, **8:** 647–654, 1954.

[6] Hueper, W. C., Wiley, F. H. and Wolfe, H. D.: Experimental production of bladder tumours in dogs by administration of beta-naphthylamine. J. Indust. Hyg. and Toxicol., **20:** 46–84, 1938.

[7] McDonald, D. F. and Lund, R. R.: The role of the urine in vesical neoplasm. 1. Experimental confirmation of the urogenous theory of pathogenesis. J. Urol., **71:** 560–570, 1954.

[8] Nelson, A. A. and Woodard, G.: Tumors of the urinary bladder, gallbladder, and liver in dogs fed o-amino-azotoluene or p-dimethylaminoazobenzene. J. Nat. Cancer Inst., **13:** 1497–1501, 1953.

[9] Bonser, G. M., Bradshaw, L., Clayson, D. B. and Jull, J. W.: A further study on the carcinogenic properties of ortho-hydroxyamines and related compounds by bladder implantation in the mouse. Brit. J. Cancer, **10:** 539–546, 1956.

[10] Walpole, A. L., Williams, M. H. C. and Roberts, D. C.: Tumours of the urinary bladder in dogs after ingestion of 4-aminodiphenyl. Brit. J. Indust. Med., **11:** 105–109, 1954.

[11] Wilson, R. H., De Eds, F. and Cox, A. J., Jr.: The toxicity and carcinogenic activity of 2-acetaminofluorene. Cancer Res., **1:** 595–608, 1941.

* 2-Acetylaminofluorene will be referred to as 2-AAF throughout the text.

[12] Cox, A. J., Jr., Wilson, R. H. and De Eds, F.: The carcinogenic activity of 2-acetylaminofluorene; characteristics of the lesions in albino rats. Cancer Res., **7:** 647–657, 1947.

[13] Dunning, W. F., Curtis, M. R. and Madsen, M. E.: The induction of neoplasms in five strains of rats with acetylaminofluorene. Cancer Res., **7:** 134–140, 1947.

[14] Dunning, W. F. and Curtis, M. R.: The role of dietary tryptophane in the incidence of 2-acetylaminofluorene-induced bladder cancer in rats. Acta Unio internat. contra cancrum, **11:** 654–657, 1955.

[15] Dunning, W. F. and Curtis, M. R.: The role of indole in incidence of 2-acetylaminofluorene-induced bladder cancer in rats. Proc. Soc. Exper. Biol. and Med., **99:** 91–95, 1958.

divided into four dietary groups (table 1). The animals were housed individually with free access to diet and water. In general, the diets were similar to those used by Dunning and Curtis. Diets F and D served as controls, respectively containing 0.06 per cent 2-AAF and no indole and 3.2 per cent indole with no 2-AAF. Diets B and E contained 1.6 per cent and 3.2 per cent of indole respectively in addition to 0.06 per cent 2-AAF. Rats on diets D and E were maintained on 1.6 per cent indole for 2 to 3 weeks to avoid the 75 per cent mortality resulting when new rats were abruptly changed from a normal diet to a 3.2 per cent indole diet. Usually, three rats from each group were sacrificed at 3-month intervals. These, together with those dying spontaneously, were autopsied with gross examination of all organs and histological examination of hematoxylin and eosin-stained multiple sections of kidneys, ureters, urinary bladder (sectioned serially), prostate, testes, seminal vesicles, heart, lungs, liver, spleen, pancreas, esophagus, stomach, large and small intestine, adrenals, trachea, thyroid, parathyroid, brain, pituitary, bone, and occasionally skin.

TABLE 1. *Composition of the diets*
(in per cent)

Diet Components	Dietary Groups			
	B	D	E	F
2-AAF	0.06	0	0.06	0.06
Indole	1.6	3.2	3.2	0
Total rats	43	71	61	71

RESULTS (TABLE 2)

In group B, with supplementation of the 2-AAF diet with 1.6 per cent indole, there was a marked increase in the average survival period (337 days) as compared with those on diet F given 2-AAF without indole (194 days). There was a total incidence of 18 bladder tumors in 31 rats (58 per cent) with 12 of the 18 tumors being carcinoma. In one animal a massive transitional cell carcinoma of the renal pelvis developed in addition to a vesical carcinoma. Only one benign bladder tumor occurred in the 6 to 9 month survival group. Liver tumors were found in 30 of the 31 animals living 6 months or longer. Of these, 16 (52 per cent) were malignant neoplasms in association with greater or lesser degrees of benign cystic disease of the liver, with eleven of the malignant tumors showing metastases. Group B was originally comprised of 43 rats. Twelve animals died or were

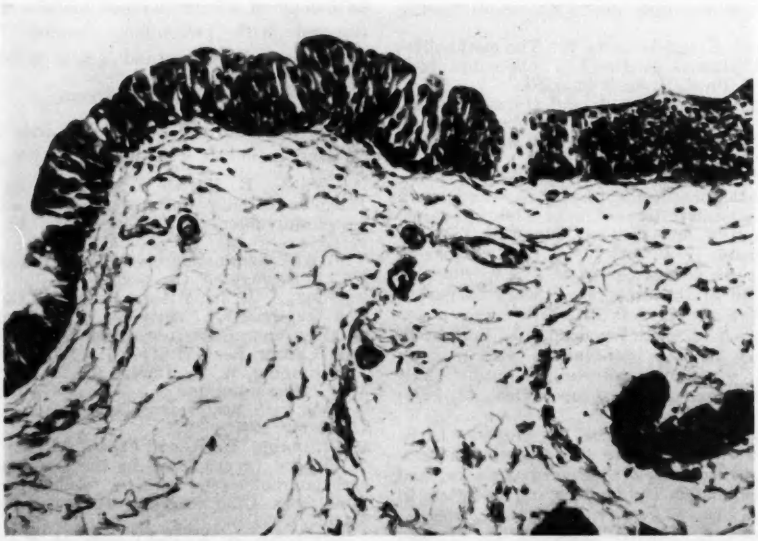


FIG. 1. Epithelium of bladder from group F rat (No. 176) at 6 months, showing early hyperplasia of epithelium with normal mucosa on right.

TABLE 2. *Summary of results*

Group		B		D		E		F	
Diet	2-AAF	0.06%		0		0.06%		0.06%	
	Indole	1.6%		3.2%		3.2%		0	
No. rats, total[a]		31		23		27		26	
Av. survival (days)		337		430		372		194	
Months on diet		6–9	10–	6–9	10–	6–9	10–	6–9	10–
No. rats per survival period		6	25	7	16	8	19	26	0
Av. survival (days)		222	366	200	545	231	426	194	0
No. of rats with bladder tumors	Benign[b]	1	5(20%)	0	0	0	3	5(19%)	0
	Malignant[c]	0	12(48%)	0	0	0	9(47%)	0	0
		12(39%)		0		9(30%)		0	
	Total	18(58%)		0		12(44%)		5(19%)	
No. of rats with liver tumors	Benign[d]	4	10(40%)	0	0	6	15(79%)	1	0
		1	15(60%)	0	0	0	4(21%)	23(88%)	0
	Malignant[e]	16(52%)		0		4(15%)		23(88%)	
	No. rats with metastases	1	11(44%)	0	0	0	0	14(54%)	0
Other neoplasms		0	1[f]	0	0	0	3[f, g]	8[h]	0

[a] Rats dying within five months were included in microscopic study but were omitted from totals.
[b] Papilloma, verrucoid lesions (severe focal squamous metaplasia).
[c] Carcinoma; one case of carcinosarcoma in group B.
[d] Duct cell cystadenoma
[e] Hepatic- and ductal-cell carcinoma, with and without benign tumors.
[f] Transitional cell carcinoma of renal pelvis.
[g] Two squamous cell carcinomas of acoustic ducts.
[h] Four squamous cell carcinomas of acoustic ducts, two leukemias, one squamous cell carcinoma of stomach, and one adenocarcinoma of small intestine.

sacrificed within five months and were included in the gross and histological studies but were omitted from the total summary of results.

Group E represented supplementation of the 2-AAF diet with 3.2 per cent indole. This group originally was comprised of 61 rats; 34 died or were sacrificed within five months and examined grossly and histologically but were not included in the total results. In the remaining 27 animals, there was an increase in the average survival period (372 days), a reduction in the incidence of liver malignancy, and an increase in the incidence of benign liver tumors as represented by benign cystadenoma of the liver. However, there was no

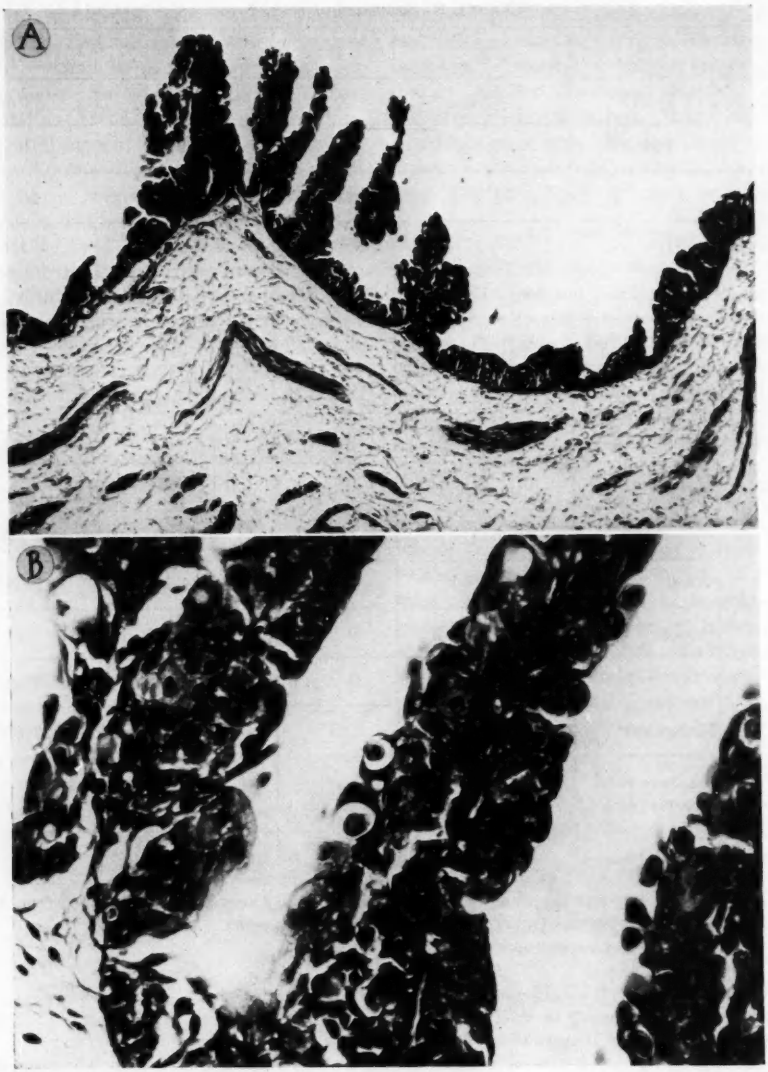


FIG. 2. *A*, papilloma of bladder in group F rat (No. 197) at 6⅓ months. *B*, higher magnification of section seen in *A*, showing dyskeratosis.

increase in the incidence of bladder tumors with 12 of the 27 animals having vesical lesions, none occurring in the 6 to 9 month survival period. Nine of the tumors were carcinomas. Liver tumors occurred in 25 of the 27 animals, but only four of these were malignant (15 per cent).

Group F animals received 0.06 per cent 2-AAF without indole. Seventy-one rats were given this diet with 45 dying within five months. These animals were examined grossly and histologically but were not included in the total results. None of the rats survived beyond 9 months, with 26 dying in the 6 to 9 month period. In this group, death was primarily due to hemorrhage secondary to rupture of massive hepatomas (88 per cent). Only five benign vesical papillomas were found in

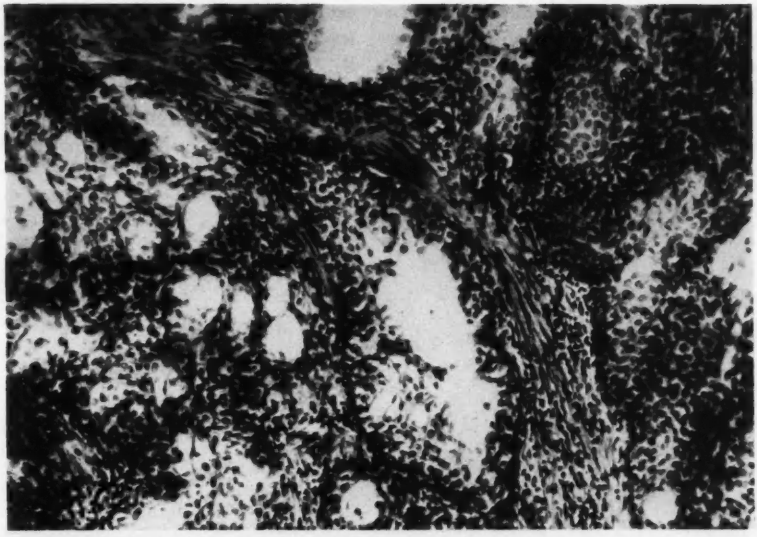


FIG. 3. Photomicrograph of invasive transitional cell carcinoma of bladder in group B rat (No. 44) at 11⅔ months.

this group. However, other tumors were found including four squamous cell carcinomas of the acoustic duct, one squamous cell carcinoma of the stomach, one adenocarcinoma of the small intestine, and two leukemias.

Group D received 3.2 per cent indole without 2-AAF. Originally, it was comprised of 71 rats with an early higher mortality unless the diet was decreased initially to 1.6 per cent indole for 2 to 3 weeks before conversion to the 3.2 per cent dose of indole. Twenty-three rats survived 6 months or longer and showed no evidence of tumor development in any organ. The survival rate of this group was the longest in the series, averaging 430 days.

BLADDER

Of the 35 instances of bladder tumor development, none appeared prior to 178 days, and 47.2 per cent appeared in 365 days.

Areas of focal hyperplasia of the epithelium was the earliest noted appearance of these lesions (fig. 1) and occurred in the sixth month of group F (0.06 per cent 2-AAF) with rapid progression to either squamous metaplasia or transitional cell papilloma (fig. 2). The development of similar changes in group B (1.6 per cent indole and 2-AAF) and group E (3.2 per cent indole and 2-AAF) was delayed until the ninth month. These changes were characterized by increased cytoplasmic content of the cell and enlargement and vesiculation of the nucleus with projection of the cells above the epithelial surface. As this growth progressed, a capillary vascular supply could be seen entering the hyperplastic cell mass from the submucosa. Once this vascular supply was established, rapid cellular proliferation occurred. After

FIG. 4. Section of bladder in group E rat (No. 241) at 14 months, showing squamous cell carcinoma with marked keratin formation.

the tenth month, these tumors became carcinomas in 48 per cent in group B and 47 per cent in group E animals. These malignant bladder tumors included transitional cell (fig. 3) and squamous cell carcinoma (fig. 4) both separately and mixed (fig. 5); adenocarcinomatous forms in which the acinar structures appeared to be composed of transitional cells; and one carcinosarcoma (group B). Tumors restricted to the mucosa and submucosa were the rule in both the transitional and squamous lesions. In 21 instances of bladder carcinoma, only seven invaded the bladder muscle

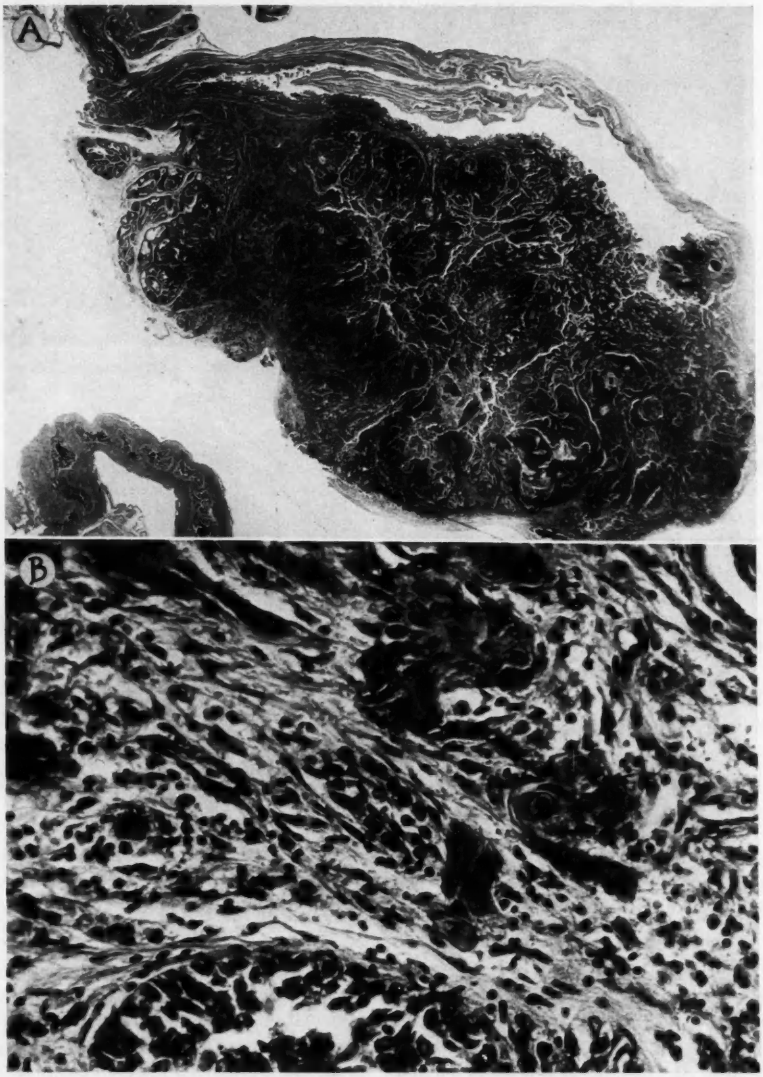


FIG. 5. *A*, photomicrograph of bladder in group E rat (No. 156) at 11 months, showing massive tumor composed of both transitional and squamous cell carcinoma. *B*, higher magnification of *A* with both transitional and squamous cell carcinoma.

and less commonly the prostate. There were neither regional lymph node nor distance organ metastases from the bladder tumors.

Two instances of transitional cell carcinoma of the renal pelvis occurred (fig. 6), one each in groups B and E, and each occurred in association with large bladder tumors with partial obstruction of the ureterovesical orifice.

LIVER

The earliest and most extensive liver changes occurred in rats of group F (2-AAF without in-

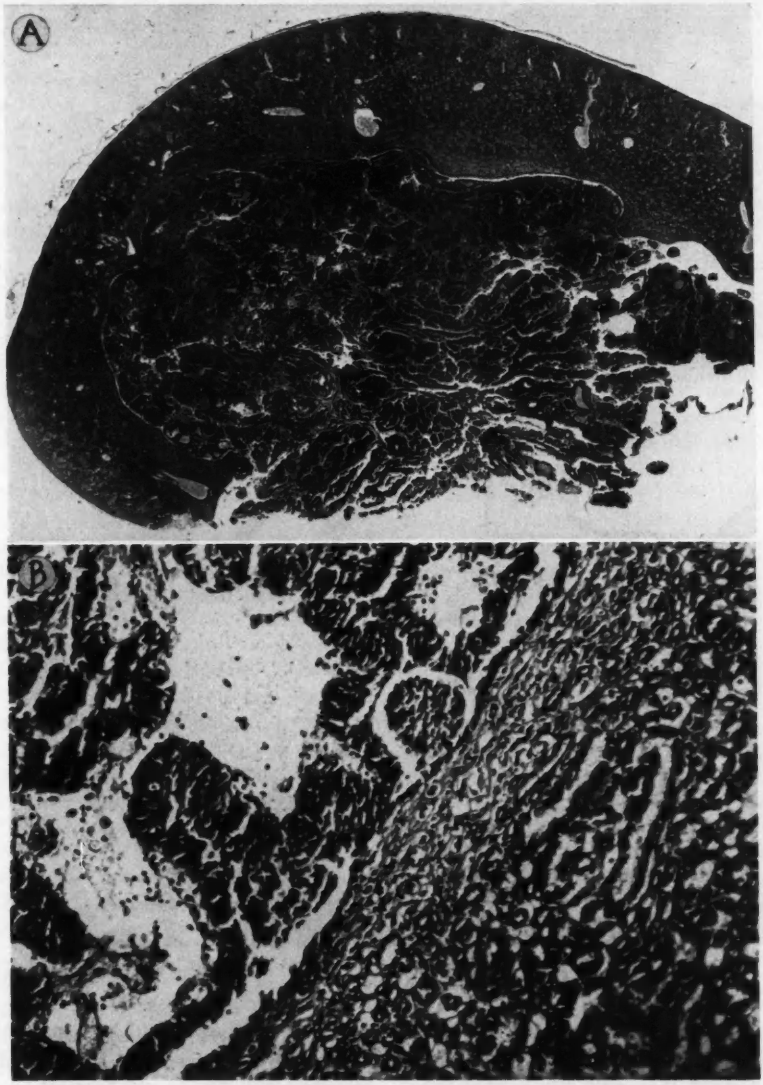


FIG. 6. *A*, photomicrograph of kidney in group B rat (No. 40) at 12 months, showing transitional cell carcinoma of renal pelvis. *B*, higher magnification of *A*, showing papillary carcinoma of renal pelvis.

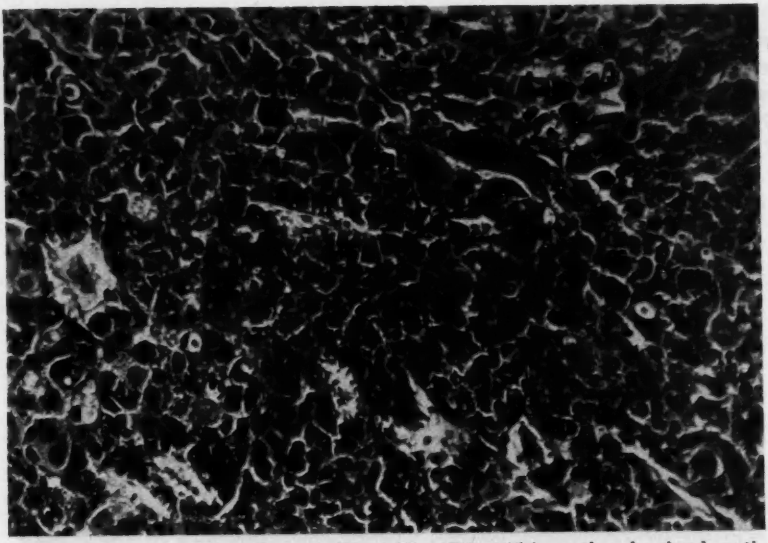


FIG. 7. Photomicrograph of liver in group F rat (No. 176) at 7½ months, showing hepatic cell carcinoma with frequent tumor giant cells.

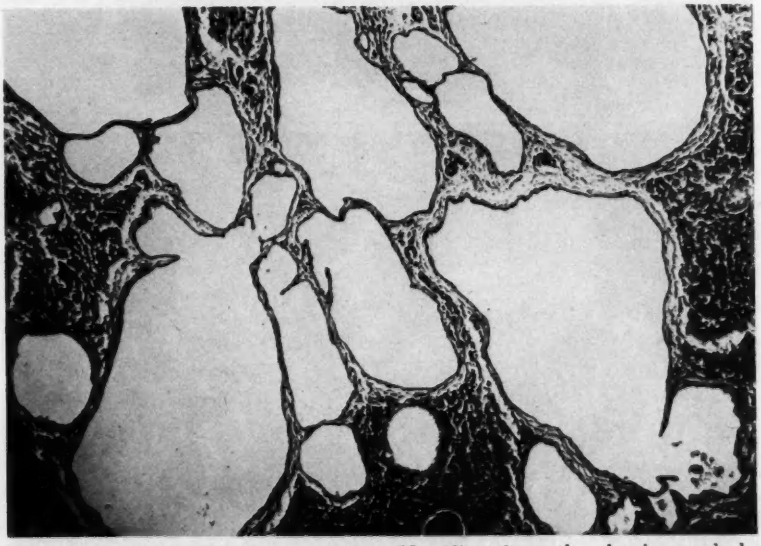


FIG. 8. Photomicrograph of liver in group B rat (No. 32) at 9 months, showing marked cystic degenerative changes, cysts being lined by cuboidal cells.

dole). These began as early as the third week as metaplastic changes of the hepatic cells which continued through the second and third months. In the fourth month, regenerating hepatic cell nodules dominated the cytological picture. Malignant changes occurred during the sixth month with development of hepatic and ductal cell carcinoma (fig. 7) and frequent co-existing benign cystadenoma.

Group B (1.6 per cent indole and 2-AAF) and

E (3.2 per cent indole and 2-AAF) differed from group F in a decreased incidence, delay in development, and diminished severity of liver alterations. The metaplasia occurred in the second month in group B and in the third month in group E. Ductal cell proliferation was the predominant feature leading to cystic dilatation in the sixth and seventh months. Benign cystadenomas (fig. 8) were present in group B from 6 to 9 months with hepatic cell carcinoma developing after 10 months (60 per cent). In group E benign cystadenoma was the only lesion well beyond the 10 month period (79 per cent).

TABLE 3. *Liver damage vs. bladder tumor in rats surviving over nine months*

Estimated Functional Liver Tissue	Group					
	B		E		Total (B + E)	
	No. of rats	Bladder tumor	No. of rats	Bladder tumor	No. of rats	Bladder tumor
More than 50%	6	2(33%)	7	0	13	2(15%)
Less than 50 %	19	12(63%)	15	11(73%)	34	23(68%)

DISCUSSION

This study has demonstrated several differences from the findings of Dunning and Curtis who used Fischer line 344 female rats: 1) Bladder tumors can be produced in some rats by 2-AAF alone. 2) Bladder carcinogenesis was somewhat less enhanced in our study by the addition of indole to the 2-AAF diet. 3) Indole definitely increased the survival rate of our animals with a marked modification of the hepatic lesions. It appeared that the increased survival time alone might have been the primary mode by which the indole increased the incidence of bladder tumor development.

The low incidence of bladder tumors in group F may have been largely the result of the abbreviated survival time and/or associated abbreviated total doses of 2-AAF. Cox, Wilson and De Eds fed 2-AAF diet in varying concentration up to 0.125 per cent and obtained a 21 per cent incidence of bladder tumors in rats.[12] They also found an earlier and higher tumor incidence in the rats receiving the largest total dose of 2-AAF. However, Dunning and Curtis were able to increase the survival time and the total dose of carcinogen in Fischer rats on an 0.06 per cent 2-AAF diet from 349 to 409 days by adding high nucleic acid yeast to the diet without production of bladder tumors.[16] They view this as strengthening their interpretation of a direct action of indole on the bladder carcinogenicity of 2-AAF apart from any effect on survival time.

In groups B and E receiving indole and 2-AAF, the development of bladder tumors was associated with liver involvement and most frequently associated with the more extensive liver lesions. Morris, Wagner and Lombard found that rats ingesting 2-AAF had a decrease in liver excretion of rose bengal beginning in the fourth week, with little or no liver clearance after 6 to 8 weeks.[17] This coincided with the replacement of functional hepatic tissue by connective tissue, pseudotubules, hyperplastic hepatic nodules, and carcinoma. In addition, it has been shown that removal of 75 per cent of the liver in normal rats can be compatible with life.[18, 19] It is probable that as much decrease in liver function produced by neoplastic disease will not cause death. With these observations in mind, each rat in groups B and E was evaluated for degree of liver damage as estimated by gross and histological examination. Hepatic destruction of 50 per cent was chosen for an index value. By this evaluation, the bladder tumor incidence was much greater in rats with less than 50 per cent remaining liver tissue (table 3). This is admittedly not a precise method of evaluating residual functional hepatic tissue; however, it was rather consistently possible to determine which animals would have bladder tumors from the histological evaluation of the liver tumors. Nonetheless, it is our opinion that

[16] Dunning, W. F. and Curtis, M. R.: Effect of a high protein and high nucleic acid diet on occurrence of 2-acetylaminofluorene-induced cancer in rats. Proc. Soc. Exper. Biol. & Med., **99**: 88–91, 1958.

[17] Morris, H. P., Wagner, B. P. and Lombard, S. L.: A comparison of impaired function with morphological changes occurring in livers of rats ingesting n-2-fluorenylacetamide. J. Nat. Cancer Inst., **20**: 1–35, 1958.

[18] Higgins, G. M. and Anderson, R. M.: Experimental pathology of the liver. 1. Restoration of the liver of the white rat following partial surgical removal. Arch. Path., **12**: 186–202, 1931.

[19] Mann, F. C., Fishback, F. C., Gay, J. G. and Green, G. F.: Experimental pathology of the liver, studies III, IV and V. Arch. Path., **12**: 787–793, 1931.

there exists a positive correlation between extensive decrease in functional liver capacity and bladder tumor development with less mild liver damage associated with an absence of bladder tumors rather than an earlier or less frequent neoplastic change.

In addition, there appears to be a positive correlation between benign cystadenoma of the liver and indole- and 2-AAF-induced bladder tumors. Almost all rats receiving these diets had cystic lesions of the liver in varying degrees. These animals have the highest incidence of bladder tumors, while rats in group F (2-AAF only) had both a low rate of bladder tumor formation and much less extensive cystic lesions of the liver. This suggests the possible participation of this form of neoplastic liver tissue in an abnormal process of metabolism of 2-AAF to a bladder carcinogen. There is the possibility that a severely damaged liver might allow an unmetabolized 2-AAF to enter the urinary tract as an active carcinogen, though Bonser has questioned the direct carcinogenicity of 2-AAF of the basis of pellet implantation tests in the mouse bladder.[20]

Certain tryptophan metabolites (ortho-hydroxyamines) have been demonstrated to be bladder carcinogens by implantation in the mouse bladder.[21, 22] It has also been shown that some human patients with spontaneous bladder cancer excrete higher concentrations of certain of these tryptophan metabolites in the urine than does the normal individual.[23-25] However, the view that tryptophan may be carcinogenic, through the addition of its metabolites to the total carcinogenic dose, is not supported by this study since feeding indole in large quantities (group D) produced no neoplastic change in any organ.

A possible action of indole may be in increasing the amount of tryptophan in the body through its inhibition of tryptophanase which acts to metabolize tryptophan to indole, pyruvic acid, and ammonia.[26, 27]

For general speculation, one may consider that excess tryptophan, from whatever source, may act to enhance 2-AAF bladder carcinogenesis by 1) increasing absorption of the carcinogens, 2) retarding the excretion of the carcinogens and increasing the tissue concentration, 3) increasing the metabolic conversion of 2-AAF to the actual bladder carcinogen(s), 4) increasing sensitivity of the bladder epithelium to the carcinogen, and/or 5) protection of the liver against the severe ravages of 2-AAF with consequent prolonged survival time and increased exposure of the bladder to the carcinogen.

SUMMARY

Charles River W (Wistar) male rats were fed synthetic diets containing 0.06 per cent 2-AAF. To two of the dietary groups, 1.6 per cent and 3.2 per cent indole was added. Rats ingesting 2-AAF alone died within 7½ months; the average survival was much longer in the groups receiving indole. The incidence of bladder tumors was higher, but the onset was delayed, when indole and 2-AAF were given together. As the amount of indole was increased, benign tumors of the liver became more common with a concomitant decrease in malignant liver neoplasm. The greater the extent of functional liver damage, the higher was the incidence of bladder tumor development. No tumors were observed in rats fed indole without 2-AAF.

Benign cystadenoma of the liver was a prominent finding in most animals that developed bladder tumors. On the basis of this study, it is suggested that there is a positive causal relationship between liver injury and 2-AAF/indole-induction of bladder tumors, and that cystadenomatous neoplasia may be involved in an altered metabolism of 2-AAF with the production of a larger quantity or a more active bladder carcinogenic agent(s).

[20] Bonser, G. M.: Unpublished data, cited in Boyland, E.: The biochemistry of cancer of the bladder. Brit. M. Bull., **14:** 153–158, 1958.

[21] Allen, M. J., Boyland, E., Dukes, C. E., Horning, E. S. and Watson, J. G.: Cancer of the urinary bladder induced in mice with metabolites of aromatic amines and tryptophan. Brit. J. Cancer, **11:** 212–228, 1957.

[22] Boyland, E. and Watson, J. G.: 3-hydroxyanthranilic acid, a carcinogen produced by endogenous metabolism. Nature, **177:** 837–838, 1956.

[23] Boyland, E. and Williams, D. C.: 34th Rept. Brit. Exp. Cancer Campaign, p. 39, 1956.

[24] Boyland, E. and Williams, D. C.: The metabolism of tryptophan. Biochem. J., **64:** 578, 1956.

[25] Brown, R. R.: The isolation and determination of urinary hydroxykynurenine. J. Biol. Chem., **227:** 649–652, 1957.

[26] Dawes, E. A. and Happold, F. C.: The tryptophanase-tryptophan reaction. 9. The natural characteristics and partial purification of the tryptophanase complex. Biochem. J., **44:** 349–361, 1949.

[27] Gooder, H. and Happold, F. C.: The tryptophanase-tryptophan reaction. The nature of the enzyme-coenzyme-substrate complex. Biochem. J., **57:** 369–374, 1954.

SUPERVOLTAGE COBALT-60 TREATMENT OF BLADDER CANCER: PALLIATION OR CURE?

LEONARD M. LIEGNER AND JOHN A. TAYLOR WITH THE ASSISTANCE OF NORMAND J. MICHAUD, B.S.

From the Radiation Therapy Section, Department of Radiology; and Department of Urology, St. Luke's Hospital, New York, N. Y.

Enormous effort has been exerted over the past years by radiation therapists and urological surgeons in their struggle to control bladder cancer. The hoped-for strides have not been realized. The over-all cure rates expressed as 3 and 5 year survivals are not enviable achievements.

Prior to the era of radical surgery, knowledge of the invasive and metastatic avenues of spread of bladder cancer was limited. Clinical estimates of the extent of the disease in the earlier years were inexact as to clinico-pathological stage. Radiotherapeutic results of necessity were lumped together irrespective of the staging of the disease and histological grade of the tumor. Gross survival rates so reported were low. Unfortunately, survival figures reported in this manner are still quoted today as the ultimate to be expected from radiation therapy.

In the past decade radical surgical techniques have been developed for excision of bladder cancers. These techniques were made feasible by excellent anesthesia, blood replacement and antibiotics which became available. The evaluation as to whether or not radical surgery has taken its place as the preferred treatment of bladder cancer is not within the scope of this paper.

Current dissatisfaction with the radical surgical approach is rising, with effort being directed to preoperative irradiation, in centers previously devoted solely to the radical surgical approach.

A secondary gain of this interest in the surgical approach to bladder cancer has been the refinement in the clinico-pathological staging of bladder tumors. Based on autopsy and surgical material, survival statistics could now for the first time be correlated with the extent of the disease.

The challenge of adequate clinico-pathological staging continues to confront those treating bladder cancer. In virtually all instances staging is retrospective. The urological surgeon with bladder and lymph nodes in hand stands serenely aloft, certain of his statistics. On the other hand, the radiation therapist and his urological colleague, committed to a more conservative course, are limited by what they can clinically assess.

Jewett's observations relating depth of bladder wall invasion to survival remain valid and form the basis of the generally accepted bladder staging of Whitmore and Marshall. The logical aspects of their bladder staging so inviting, that we all tend to lose sight of Marshall's statement that "no one knows what proportion of vesical cancers fall into what exact stage at the time patients present themselves for treatment." How then may we narrow down the margin of error in pre-treatment staging?

We would like to re-emphasize the importance of Jewett's conclusion that the pre-treatment clinical pathological staging depends on two findings: 1) the presence or absence of bladder wall induration estimated by a bimanual examination under anesthesia; induration being tantamount to deep muscle or paravesical invasion, 2) a deep biopsy of the bladder tumor isolated from other specimens, which correlates well with the findings in bimanual examination. Baker also advises isolation of a deep biopsy. From our own experience, the urologist's estimation of the depth of the tumor during a transurethral resection also has great validity in determining invasion. This is supported by Melicow who has painstakingly shown that "biopsy usually helps determine the grade of malignancy and may reveal local infiltration; it cannot establish whether the tumor has grown through the bladder wall. *It remains for the urologist to determine by clinical and operative procedures whether or not extramucosal involvement has occurred.*"* Melicow continues by stating that "except for grades 1 and 4, i.e. early or late malignancy, biopsy finding can guide operative pro-

* Italics are ours

cedures to a limited degree only." He concludes that "grading of bladder tumors is of value from the point of view of statistics and pathology and that the sole dependence on it for treatment and prognosis is unwise."

In our study mention will be made of the location of the bladder tumor and its size. In many reports on the results of treatment, size and location of the tumor are not described (16, 5, 6, 8, 9); in others their importance is recognized (7, 3, 18). Anatomical location of the bladder tumor and its relationship to regional nodal metastases was emphasized by Jewett in his autopsy study. He showed that in patients who had died immediately after operation, posterior bladder wall invasion was associated with a lower incidence of nodal metastases than with cancer invading other walls.

Baker studied whole bladder sections and discovered that circumferential spread of the tumor with skip areas takes place. How distant circumferential spread occurs from the primary tumor was related to the depth of invasion and the diameter of the base of the mucosal lesion. The degree of circumferential spread cannot be determined with accuracy clinically.

Some authors (Friedman; Rubin and Buran) in subdividing their material by clinico-pathological stage and histological grade give the impression that histological grades 3 or 4 invariably fall into the more invasive clinical stages, whereas histological grade 1 or 2 is always correlated with less invasive tumors. Rubin and Friedman have both shifted stage OAB_1 tumors, grade 3 or 4, to stage B_2C. We have not done this since our thinking is in agreement with Jewett who stated that "correlation of the microscopic anatomic structure of infiltrating tumors with the depth to which they had penetrated the bladder wall demonstrated that, with the exception of undifferentiated carcinoma, tumors of similar types were present in the superficial infiltrating as in the deeply infiltrating groups."

Our series of cases has been retrospectively staged and graded only on the clinico-pathological facts actually observed and recorded. We believe that retrospective staging in bladder cancers should be weighted to the more favorable stage rather than placing cases in the more advanced stages without clinico-pathological support. Not to do so can only diminish the confidence in the statistics presented as evidence in support of a particular treatment method. We do make a plea, however, that urological surgeons performing radical operations, and not limited by the staging deficiencies imposed upon those treating more conservatively, interpret radiotherapeutic results with a more understanding attitude.

MATERIAL

Between November 1954 and December 1959, a total of 127 primary bladder tumors were admitted to St. Luke's Hospital, N. Y. Eighty-eight (69.2 per cent) of 127 patients were treated by combined transurethral resection and radiation therapy.

Forty-two of the 88 patients had treatment directed to the bladder alone using combined transurethral resection and external supervoltage cobalt-60. These 42 cases so treated are the basis of our presentation. No patient was refused treatment. In the 46 other patients comprising the balance of the 88 cases, the bladder and pelvic lymph nodes were both included in the field of irradiation and will be the subject of a future report.

The sex distribution of the 42 cases conforms to the known incidence: 28 were males, 14 females. Thirty-nine were white, three Negro. The predominance of white patients reflects the hospital population. The shift towards patients in the older age groupings is typical of bladder cancer. There were 8 patients 40–60 years old; 19 patients 60–70 years old; 12 patients 70–80 years of age, and 3 patients over 80 years. Therefore, 34 of 42 patients (80 per cent) were beyond 60 years of age.

TUMOR GRADING

The different tissue types and number of cases of each comprising our series of bladder tumors were as follows: transitional cell, 32 cases (76 per cent); epidermoid, 6 cases; undifferentiated, 4 cases.

Our pathologist* is guided in his grading of bladder tumors by three criteria: 1) over-all histological morphology of the tumor, 2) specific cellular alterations malignant in character, 3) evidence of tumor infiltration into or through the muscularis if such evidence is present in the specimen. Histological proof of muscularis invasion converts a tumor considered low grade

* Dr. Charles Begg, Director of the Department of Pathology.

on the basis of criteria 1 and 2 to a high grade tumor. The chance absence of muscularis invasion in a slide would require a low grade classification of the tumor though in fact the tumor later proved to be infiltrative. The breakdown of our cases by grade shows that this last possibility affects only a small number of the total tumors seen by us: grade 1, 4 cases; grade 2, 2 cases; grade 3, 20 cases; grade 4, 10 cases; undifferentiated, 4 cases; not described, 2 cases.

PREVIOUS TREATMENT

Unlike Friedman whose bladder material contained a high number of recurrent tumors (75 per cent) following prior curative attempts by excisional surgery or radiation, our cases are favorable in this regard. Transurethral resection was the only treatment that preceded radiation. In 41 of 42 patients transurethral resection was performed once in 18 cases and twice in 10 others. Transurethral resection was carried out within days to weeks of irradiation in 31 patients; between 1–3 months in 7 patients and between 3–6 months in four others. Eight other patients of the 42 underwent from 3 to 6 transurethral resections preceding the final pre-radiation procedure. One patient underwent transurethral resection every month for more than a year. In the records of 5 patients no statement was made in regard to the number of transurethral resections before the final fulguration. None of the 42 patients had undergone prior surgery or radiation save one who had a segmental bladder resection with radon seed implantation 6 months before combined transurethral resection and radiation therapy.

DISTRIBUTION OF CASES BY STAGE AND GRADE

In this series of bladder cases, staging was determined retrospectively since there were no patients in whom the stage of the disease was recorded according to the Jewett and Whitmore-Marshall schema, at the time of therapy. As mentioned in the introduction, we restaged cases in a conservative manner, favoring a less infiltrative stage. We utilized multiple criteria: 1) the cystoscopist's evaluation and description of the tumor during transurethral resection, 2) bimanual examination under anesthesia if described and 3) evidence of invasion into the muscularis in the microscopic section.

Table 1 shows that 40 per cent were superficially infiltrative tumors, 26 per cent deeply infiltrative. The 21 per cent in which the stage was not described could affect significantly the percentage of deeply infiltrative tumors. We make a special plea that the cystoscopist record the information so as to reduce as much as possible this relatively large group in which even retrospective staging could not be determined. Another point of note in table 1 is the 80 per cent incidence of high grade tumors, 28.5 per cent of which were stage AB_1, 35.7 per cent stage B_2CD.

TABLE 1. *Distribution of 42 cases of bladder cancer by stage and grade*

Grade	Stage							Total
	Superficial			Deep				
	O	A	B_1	B_2	C	D	Not desc.	
Low (1, 2)	0	4	1	1	0	0	1	7 17%
High (3, 4, undiff.)	0	4	8	8	2	5	8	35 80%
Total	0	8 40%	9	9 26%	2	5 11%	9* 21%	42

* One case not described (grade)

GROSS CYSTOSCOPIC DESCRIPTION BEFORE COBALT-60 IRRADIATION

The bladder tumors occupied a single area in 16 cases; multiple discrete areas in 11 cases; multiple contiguous areas in 17 cases. The site of the tumor was not determined in 8 cases, usually being described as "filling the entire bladder." The following anatomical sites were mentioned as containing tumors in the frequency listed, either as single area or as an area of involvement continuous with other sites: lateral wall, 18 times; trigone, 6 times; base, 6 times; neck, 5 times; posterior wall, 6 times; dome of bladder, 3 times.

Areas of the bladder other than posterior wall were involved a total of 35 times compared to the posterior wall and dome which were occupied by tumor 6 and 3 times respectively. Tumors other than posterior wall lesions have a higher frequency of regional nodal metastases (Jewett and Strong).

Table 2 correlates the tumor location, whether unilateral, bilateral or midline, with the trans-

TABLE 2. *Description of bladder tumors prior to cobalt-60 irradiation during transurethral resection*

Bladder Location	Infiltration		Size		Not Described Infilt. &/or Size
	Yes	No	Large	Small	
Unilateral 36% 15	8	1	11	2	8
Bilateral 24% 10	3	3	7	3	4
Midline 29% 12	8	2	10	1	3
Not descr. 11% 5	1	4			
Total	20	10	28	6	15

TABLE 3. *Urologist's estimate of infiltration determined during pre-irradiation transurethral resection compared to final pathological grading*

Grade	Infiltration	Non-infiltration	Not Described	Total
1	3	1		4
2		1	1	2
3	12	3	6	21
4	6	1	3	10
Undiff.	1		3	4
Not desc.			1	1
Total.....	22	6	14	42

urethral resection estimate of infiltration and size of the tumor. When the location was specified, the tumor was bilateral or midline in 22 cases.

The cystoscopist described 20 infiltrative tumors and 28 large tumors. In 15 cases infiltration and/or size were not mentioned. In 12 the tumor was either non-infiltrative and/or small.

The retrospective staging shown in table 1 is consistent with the contents of table 2.

The urologist frequently consults with the radiation therapist at the completion of his transurethral resection and before the pathology report is available in those patients whose tumor he estimates has infiltrated the muscularis. Table 3 shows pre-irradiation transurethral resection estimate of infiltration. It is noteworthy that when the cystoscopist estimates infiltration, this fact correlates well with the high grade (3, 4, undiff.) reported by the pathologist.

Nineteen of 22 tumors judged as infiltrative were high grade cancers. In only 3 cases the pathologist reported a low grade tumor whereas the cystoscopist had reported infiltration during fulguration.

Table 3 confirms Melicow's insistence that the urologist's evaluation of the extent of the tumor invasion be given greater weight.

IRRADIATION FACTORS

Stationary external supervoltage cobalt-60 irradiation was the modality used in all patients. Source skin distance was 80 cm.

Treatment fields encompassed the entire bladder but did not include the regional pelvic nodes. As discussed earlier under transurethral resection, bladder irradiation was started within a short time following fulguration in the majority of cases. Anterior three field placement was used in 33 patients with the lateral two fields angulated 45–55 degrees towards the bladder. The angulation of fields varied with the patient's cross-section dimensions and bladder location. Two anterior field placements were used in 8 patients, and in a single patient 180 degree anterior rotation was employed.

Immediately before each treatment session patients were directed to void. The bladder base was considered to be anterior to the midplane of the pelvis; although in some patients a more anterior location was ascertained after a cystogram was taken in the lateral projection using skin markers anteriorly and posteriorly. Each patient's own cross-section was used to reconstruct the location of the bladder.

The calculated tumor dose in the bladder varied from 10–15 per cent between the minimum and maximum values. The minimum tumor dose was just under 6,000 r in 10 patients; 6,000 r in 30 patients, and over 6,000 r in 2 additional patients.

The over-all time of treatment was under 6 weeks in 12 patients; 6 weeks in 22 patients and greater than 6 weeks in 8 others.

The size of each field was smaller than 8 by 10 cm. in 3 patients; was 8 by 10 cm. in 30 patients and greater than 8 by 10 cm. in 9 others.

SYMPTOMS ATTRIBUTABLE TO COBALT-60 IRRADIATION

The delivery of a cancerocidal dose to the bladder must be accompanied by increased urinary and bowel symptoms. However, symp-

toms occurring during irradiation are not solely radiation-induced in every instance. In our experience pre-existing infection and bladder neck contractures secondary to transurethral resection are important etiologic factors. The control of infection or subsequent correction of bladder neck contracture cures what is frequently glibly attributed to radiation cystitis by the novitiate.

The evaluation of radiation-induced symptoms depends upon the quantitative estimation of pre-existing symptoms recorded in the patient's history. This is rarely available.

In our series 32 of 42 patients had pre-existing hematuria. In 25 of the 32 this was the sole symptom. Thirteen other patients had multiple symptoms of urgency, frequency, dysuria and nocturia. In one patient, pain and in another patient, frequency were the only complaints. In 9 of 10 patients with frequency this was an associated symptom. Dysuria, urgency and nocturia were always part of a symptom complex. Dysuria was recorded 10 times, urgency twice, and nocturia on 3 occasions.

SYMPTOMS DURING BLADDER IRRADIATION

In 7 patients there was no aggravation of pre-existing symptoms. In 31 patients symptoms were increased, ranging between moderate and severe in 27 of these. In 16 of the 31 patients with aggravated symptoms, diarrhea was associated and in nine of the 16 patients, diarrhea preceded urinary symptoms by 1,000–3,000 r tumor dose. In 4 patients no evaluation could be made.

The tumor dose at which urinary symptoms first appeared is given as follows: 5 cases, under 2,000 r; 11 cases, 2,000–4,000 r; 12 cases, 4,000–6,000 r. In two additional patients the dosage was not stated.

Following the completion of irradiation 23 patients had persistent symptoms; in 13 of these patients urinary symptoms without demonstrable radiation cystitis persisted 3–6 months. In 10 of the 23 patients urinary symptoms associated with cystoscopically verified radiation cystitis continued 6–12 months beyond the course of cobalt therapy. Twelve patients were symptom-free. In seven additional patients no evaluation was possible.

Knowledge of the response of bladder tumors to irradiation is limited by the cautiousness with which one approaches the cystoscopic examination of an acutely reacting bladder. In general, cystoscopy should be judiciously withheld unless definite indication exists for the examination such as continued bleeding.

TABLE 4. *Complications due to cobalt-60 irradiation*

None	24	
Bladder		
Cystitis protracted	5	33%
Cystitis + necrosis	1	
Cystitis + contracture	3	
Contracture alone	4	
Vesicocolic fistula (healed)	1	
	14	
Skin		
Moist desquamation (healed)	1	
Subcut. fibrosis (chronic)	3	
	4	

In our series cystoscopy was performed during the course of cobalt therapy on 3 patients. In 25 others cystoscopy was done 1 to 6 months after the completion of treatment; in 4 others, between 6 months and 2 years. Fifteen of the 32 patients had multiple examinations after the completion of irradiation.

The response of the tumor could not be evaluated in 9 patients. In one of the 3 patients examined during therapy, the tumor remained unchanged. In the period following therapy 4 tumors had progressed; 5 tumors had partly regressed and 23 (approximately 55 per cent) tumors had completely regressed (72 per cent of those in whom evaluation was possible).

We can accept from the foregoing that irradiation can temporarily control the local lesion in at least half of the treated patients. However, the radio-responsiveness observed does not permit us to prognosticate which patients will survive their disease.

Treatment following combined transurethral resection-cobalt-60 irradiation was: no further treatment, 26 cases; additional transurethral resection, 7 cases; deep x-ray therapy to metastases, 1 case; ileal bladder and cystectomy, 1 case; intracavitary radium, 2 cases; resection of contracted vesical neck, 1 case; hospitalization for bladder infection, 4 cases.

Table 4 lists the complications attributed to

cobalt-60 irradiation. The over-all incidence of bladder complications of all types was 33 per cent. Of these 14 complications, nine (21 per cent) were serious but did not cause death. One of the contracted bladders was resected, as just stated. The vesicocolic fistula eventually spontaneously closed. Three patients had mild, chronically persistent subcutaneous fibrosis. The complication rate we observed truly reflects what occurs consequent to bladder irradiation. In most publications (Browne and Ogden; Rubin and Buran) complication rates are based on the number of patients rather than the incidence. These authors refer to those major complications contributory to the death of patients. Serious reactions expressed in this manner rarely give rates above 10 per cent.

Cox reports his over-all complication rate as 34 per cent (20/58), Browne and associates and Rubin and associates, although isolating the major from the over-all complications, do report 51 per cent and 55 per cent radiation cystitis as occurring in their cases. These figures are in agreement with our report.

SURVIVAL

Bladder cancer survival statistics have been reported in many ways. Some are valid within limits, others are totally misleading. If one reports 3 and 5 year survivals by the direct or ad hoc method (Berkson and Gage), weight is given to only those patients who have been treated 3 and 5 years previously. By so doing a number of patients are eliminated from the total experience who have actually survived significant increments of time up to the year selected for analysis and whose survival has not been accounted for in the survival figure. This also applies to patients lost to followup study at various intervals up to the time of reporting.

We have used the actuarial method of Berkson which, unlike the direct methods, utilizes maximally the total patient experience in any study.

Figure 1 is based on the actuarial method. The lower curve shows the percentage of patients in our series surviving yearly up to the end of 3 years. The upper curve shows the survival rates for a normal population of the same average age as our patients succumbing to causes other than cancer. By correcting the lower curve for deaths that would be expected due to causes other than cancer, we arrive at a survival rate of 36.6 per

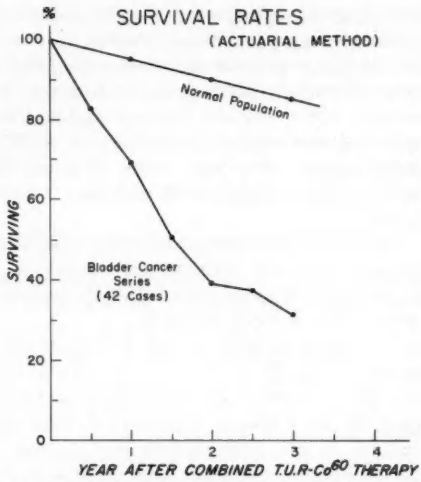


FIG. 1. Percentage of patients with bladder cancer who, after having been treated with combined transurethral resection-cobalt-60 irradiation, survived for various periods. These percentages are compared with similar percentages of survival of normal persons of same average age as cancer patients. To find age-adjusted survival rate for our cancer group at 3 years, divide survival rate of cancer group by survival rate given at corresponding point of general curve; this fraction can be considered the age-adjusted survival.

cent, rather than the uncorrected rate of 31.4 per cent which represents death due to cancer and all other causes combined. The corrected rate is comparable to cystectomy survival rates.

Table 5 gives the 3 year survival by stage and grade. Regardless of histological grade no patients who had deeply invasive or metastatic bladder cancer survived 3 years. On the other hand, 75 per cent* of those with early invasive, low grade tumors survived 3 years whereas 50 per cent* of those with early invasive but high grade tumors survived for the same interval. Two additional patients in whom the stage could not be determined but whose tumors were high grade also survived 3 years. These 3 year rates surpass those reported in cystectomy (Marshall; Whitmore and Marshall) and radiation series (Friedman; Rubin and Buran). If we had staged our cases less conservatively, these values would be lower but likewise the salvage of patients in the deeply invasive group would be greater and probably like the published percentages.

* These percentages are extremely unstable because the total number of patients observed was small.

TABLE 5. *Three year survival of patients with bladder cancer, based on stage and grade*

Grade	Stage			Not Described
	A-B_1	B_2-C	D	
Low (1, 2)	4(3) 75%	1(0)	—	1*(0)
High (3, 4, undiff.)	12(6*) 50%	9(0)	4(0)	6(2*) 33%
Total.....	16(9)	10(0)	4(0)	7†(2)

( ) = Alive

* = Not adjusted for followup losses which would increase number shown.

† = 2 additional cases dead; stage and grade not described.

CONCLUSIONS

A series of 42 bladder cancers treated with combined transurethral resection and external supervoltage cobalt-60 irradiation is presented. Thirty-six and six-tenths per cent of patients have survived their cancer 3 years irrespective of stage and grade.

Conservative retrospective staging using the Jewett and Whitmore-Marshall classifications placed 40 per cent of the cases in the superficially infiltrative stage; 26 per cent of the cases were deeply infiltrative; and 11 per cent metastatic. Aside from the stage of disease as clinically assessed, other features of the tumor such as location, size and histologic grade support our belief that the disease in our series was more advanced than could be assessed from the records. Fifty-three per cent of the cancers were midline or bilateral in location. Two thirds were described as large; and 80 per cent of the malignancies were histologically high grade.

The validity of any bladder series depends upon gathering as much information as possible before treatment is instituted. The minimal requirements should be 1) the result of the bimanual examination of the bladder under anesthesia, 2) the estimation of the degree of muscularis infiltration at the time of transurethral resection or fulguration, 3) the isolation of the deepest bladder wall biopsy for grading on the basis of morphology and evidence of muscularis invasion, 4) description of location and size of the tumor.

Combined transurethral resection-cobalt-60 treatment of bladder cancer with a technique that limits radiation to the bladder alone has failed at 3 years to salvage any patient with unequivocal deeply infiltrating cancer.

Mostofi and others (Jewett and Strong; Bloom) have shown the frequency with which distant metastases occur in bladder cancer. In the autopsies in our series we have also found extensive distant metastases clinically unsuspected. The realization that distant metastases kill the patients rather than possible local persistent disease requires a reorientation as regards bladder cancer. We believe that local, superficially infiltrative cancers, regardless of histological grade, can effectively be treated by repeated transurethral resections. Deeply infiltrative cancer of the bladder still awaits perhaps a biochemical cure. We do not feel that supervoltage irradiation directed to the bladder alone offers anything but short term palliation to this unfortunate group of patients. If any advances are to be made we believe that irradiation must be directed both to the regional pelvic lymph nodes as well as to the bladder itself. Such a study is now in progress at St. Luke's Hospital.

We wish to express appreciation for permission to include in this study the private patients of the staff of the Department of Urology, St. Luke's Hospital, in particular to Drs. George and Eugene Hoch, and Dr. Boris Petroff.

Advice for the statistical analysis was given by Phyllis B. Michelsen, Faculty of Medicine, Columbia University, New York, N.Y.

REFERENCES

BAKER, R.: Correlation of circumferential lymphatic spread of vesical cancer with depth of infiltration: Relation to present methods of treatment. J. Urol., **73:** 681–690, 1955.

BERKSON, J. AND GAGE, R. P.: Specific methods of calculating survival rates of patients with cancer. In: Treatment of Cancer and Allied Diseases, ed. by George T. Pack and Irving Ariel. New York: Paul B. Hoeber, Inc., 1958, vol. 1, chapt. 37.

BLOOM, H. J. G.: Treatment by interstitial irradiation using tantalum 182 wire. Treatment of carcinoma of the bladder: A symposium. Brit. J. Radiol., **33:** 471–479, 1960.

BROWNE, H. H. AND OGDEN, R. T.: Rotational cobalt 60 teletherapy of vesical cancer. Am. J. Roentgenol., **83:** 107–115, 1960.

BUSCHKE, F. AND CANTRIL, S.: Roentgentherapy of carcinoma of the urinary bladder. Analysis of 52 patients treated with 800 k.v. J. Urol., **48:** 368–383, 1942.

CORDONNIER, J. J. AND SEAMAN, W. B.: Betatron therapy in advanced carcinoma of urinary bladder. J. Urol., **76:** 256–262, 1956.

Cox, R.: Treatment of carcinoma of the bladder. A symposium: Treatment by 2 MeV. x-rays. Brit. J. Radiol., **33:** 480–483, 1960.

Cuccia, C. A., Jones, S. and Crigler, M. D.: Clinical impressions in 100 consecutive cases of carcinoma of the urinary bladder treated by supervoltage. J. Urol., **79:** 99–109, 1958.

Friedman, M.: Supervoltage (2 mvp) rotation irradiation of cancer of the bladder. Radiology, **73:** 191–208, 1959.

Jewett, H. J. and Strong, H. G.: Infiltrating carcinoma of the bladder. Relation of depth of penetration of bladder wall to incidence of local extension and metastases. J. Urol., **55:** 366–372, 1946.

Jewett, H. J.: Bladder cancer: The importance of biopsy and bimanual examination in clinical management. In: Proceedings of the Second National Cancer Conference, 1952. New York: American Cancer Society, 1954, pp. 375–382.

Jewett, H. J.: The surgical treatment of carcinoma of the bladder. J. Urol., **79:** 87–93, 1958.

Marshall, V. F.: Carcinoma of the urinary bladder. A perspective on radical surgical treatment. In: Proceedings of the Second National Cancer Conference, 1952. New York: American Cancer Society, 1954, pp. 382–387.

Melicow, M. M.: The bladder biopsy: An evaluation of the cystoscopic procedure. J. Urol., **56:** 339–347, 1946.

Melicow, M. M.: Tumors of the urinary bladder. A clinico-pathological analysis of over 2,500 specimens and biopsies. J. Urol., **74:** 498–521, 1955.

Morrison, R.: Carcinoma of the bladder. Its treatment by supervoltage x-ray therapy. Clin. Radiol., **11:** 125–129, 1960.

Mostofi, F. K.: A study of 2,678 patients with initial carcinoma of the bladder. I. Survival rates. J. Urol., **75:** 480–491, 1956.

Rubin, P. and Buran, R.: Supervoltage irradiation in bladder carcinoma, 1952–1958. Radiology, **73:** 209–225, 1959.

Whitmore, W. F., Jr. and Marshall, V. F.: Carcinoma of the bladder. Surg. Clin. N. Amer., **33:** 501–515, 1953.

DISCUSSION

PRESIDENT RUSCHE (Los Angeles, Cal.): As far as recurrence of carcinoma in the urethra following cystectomy, it has occurred in 2 cases that I have seen. One of these patients happened to be a doctor friend of mine who was operated upon by Dr. Cordonnier. I wondered whether he was included in any series. Both of these patients were treated with supervoltage cobalt therapy. One did not respond. Carcinoma finally took his life. The other one died spontaneously of a coronary while he was still under treatment. I have no way of judging whether there was any value to our treatment.

The other thing I wanted to say was in regard to Dr. Taylor's paper. Using cobalt, we started in exactly the same year, in 1954, along with Dr. Jaffe. We have been resecting these tumors and treating them with cobalt therapy. In the cases we thought were suitable, where we didn't have distant metastasis, we have come almost to the same conclusion: the higher the malignancy of the tumor, the more complete the local response in the bladder. But it certainly hasn't controlled distant metastasis. We hope within the next year to report our series, which is something over a hundred cases at the present time.

DR. WYLAND F. LEADBETTER (Boston, Mass.): I am particularly interested in Dr. Cordonnier's paper on the development of tumors in the urethra after cystectomy. Our experience has paralleled his.

In our series of cystectomy, we now have a total of 6 patients in whom tumors in the urethra have subsequently developed; I am sure that these tumors were not present at the time of cystectomy. This goes up to and includes 1 case of 5 years after cystectomy, which ultimately cost the life of the patient.

I realize that this is a relatively small percentage so far as the total problem is concerned. Yet this becomes, I think, a very important problem. I think we should begin to consider the definite desirability of doing urethrectomy along with cystectomy.

This is a technical problem which, unless one uses two teams for urinary diversion, is a time-consuming and pressing matter. I think we have to come to the point where we will use two teams in carrying out these operations. I don't know how one can choose on which patients one would need to do a urethrectomy; but I think all types of tumors, because we have one with superficial papillary tumor recurrence and some with infiltrating tumor recurrence. I think one probably has to plan to do the urethrectomy.

I have a few slides which show the technique we have been using for urethrectomy. I thought you would like to see them. There is nothing much to it, but this has to be done with dispatch if it is going to be done as part of cystectomy. May we see the first slide?

(Slide) This represents a long longitudinal incision made from the tip of the penis down to the base of the penis here.

(Slide) This represents establishing a line of cleavage between the corpus spongiosum and the corpora cavernosa.

(Slide) There are two problems here: One is the removal of the urethra when a non-infiltrating lesion is present; and, again, the problem of non-infiltrating lesions. I'm sure that in infiltrating lesions one has to do a complete penectomy and get back under the triangular ligament.

In the superficial lesion, this seems to work out pretty well, establishing a line of cleavage between the corpora posteriorly and the corpus spongiosum anteriorly.

(Slide) You strip this all out. It can be done in quick fashion without much bleeding.

(Slide) This represents the whole operation back to this point.

Then we change to the perineum through an inverted U.

(Slide) This is the perineal part of the incision.

(Slide) It is opened up in this fashion. You then tunnel through and pull the urethra here into the perineal wound.

(Slide) This shows the tunneling under and pulling the urethra through.

(Slide) This represents going back to and under the sepsis. This, incidentally, is the weak point of this as a secondary procedure. If the tumor has developed back in the proximal bulbous portion of the membranous urethra, it is almost impossible to know whether you are outside of the tumor or not. I think that is one reason why

urethrectomy should be done with cystectomy. If you don't do it and the tumor develops in this area, you are going to lose the patient.

(Slide) This shows a completed operation. This, I think, should take probably about 45 minutes. If it is done by a relatively fresh team, I think it can be carried out without too much trouble. I think that we are coming to this. I think as time goes on, more and more cases will be seen.

The thing that interests me primarily is what causes these tumors. Does this have any relation to urinary carcinogens? One would say offhand it doesn't; but it is possible that the changes in the urethra have taken place prior to cystectomy and that the cancer actually hasn't developed except over a considerable period of time.

In closing, I would like to ask Dr. McDonald if he has done any work on isolating or trying to isolate the compound in the rat's urine after giving 2-acetylaminofluorene that might be responsible for the development of tumors.

Dr. Harry M. Spence (Dallas, Texas): It is fun to get in a discussion of semantics with a perfectionist like Dr. Cordonnier. I think that his paper is fine, but it is mistitled. It is not Recurrences of Urethral Carcinoma Following Cystectomy for Carcinoma of the Bladder, but should be The Occurrence of Urethral Carcinoma Following Cystectomy for Carcinoma of the Bladder or Recurrence of Bladder Carcinoma Within the Urethra. The former would fit in with his theory of multicentric origin.

I have brought some slides of the operative treatment of this complication which duplicate Dr. Leadbetter's. We have had three of these cases of cancer in the urethra following cystectomy for cancer of the bladder all showing the typical clinical picture of bloody mucoid urethral discharge at varying intervals after the cystectomy. Our percentage of occurrence of this complication would be higher than that in Dr. Cordonnier's series because our number of cystectomies is far less than his. I don't know the exact number we have done, but I am sure it is well under fifty.

(Slides demonstrating Dr. Spence's technique were shown.)

While one can make a presumptive diagnosis from the history, it is desirable to demonstrate the lesion visually. I have done this by making a urethrogram under very gentle pressure. Perhaps this is not a good idea in view of Dr. Weyrauch's thoughts on dissemination of tumor cells. It is perfectly feasible to look in the remaining urethral segment with the panendoscope also, but you just get one look because the inevitable trauma soon obscures the field.

If I might presume to comment upon Dr. John Taylor's paper, had I written such a paper, I would have had to add a third word to his title, namely Aggravation. The title would then have to read Supervoltage Cobalt-60 Therapy of Bladder Cancer: Palliation, Cure or Aggravation. We have a syndrome which we call the "thimble bladder." What it amounts to is a nonusable bladder after cobalt. Perhaps our people are not as skillful at administering it as Dr. Taylor. I will say that most of the aggravated cases were in the earlier group treated. Nevertheless, I have seen a number that were made worse as far as the bladder function was concerned, although their tumor was controlled. In several of those, we have made no attempt to do a cystectomy, but have simply done an ileal loop diversion. I think that is something to consider in the management of the syndrome of "thimble bladder".

Dr. William Wallace Scott (Baltimore, Md.): I was reminded of what one of our assistant residents said about cobalt therapy. He said it produces the cobalt blues.

I enjoyed all of the papers, but I would like especially to comment on Dr. James McDonald's paper and describe in two minutes an experiment done by one of the members of our resident staff, Dr. H. John Bradley, Jr., which relates somehow to the work that Dr. McDonald has been doing. It will take one minute of explanation.

As you are all aware, Eric Boyland from the Chester Bay Research Institute showed some years ago that urinary metabolized triptothene is carcinogenic as far as the bladder is concerned in mice. These substances are conjugated as glucuronides in the urine. They must be hydrolyzed to act. They are hydrolyzed by the urinary enzyme beta glucuronidase.

1-4-Sacrolactone is a powerful beta glucuronoidase inhibitor. With this mind. Dr. Bradley came up with the idea of trying to inhibit the induction of bladder tumor with this glucuronidase inhibitor.

Specifically, what he did was to use the Dunning method of induction of bladder tumor by giving the same carcinogen that Dr.

McDonald described, 2-AAF, plus, at one point, 4 per cent triptothene in the diet. If one doesn't give the triptothene in the diet, in this instance one doesn't get bladder tumors; if one does, one gets a high incidence of bladder tumors in the Fischer 344 animals.

What Dr. Bradley did simply was to administer 1-4-sacrolactone to half the animals. Unfortunately or fortunately as the case may be, the incidence of induction of bladder tumors with this agent was not altered at all. There was not statistical difference.

As you may know, Dr. Boyland now has under way a double blind study in which half of the patients with bladder tumor are getting 1-4-sacrolactone; the others, none. As yet we have no idea whether this prevents the recurrence or not.

In the interest of economy of time, I would just like to make a couple of comments. The first is in reference to Dr. Cordonnier's paper. Our experience parallels his. We have not analyzed our material, so I can't give you a percentage figure regarding the incidence of urethral recurrences following cystectomy, but I would judge from a rough estimate that our data would correspond very much to his.

We have done urethrectomies in conjunction with cystectomy in male patients with multiple papillary tumors of the bladder because it has been our impression that most of the urethral recurrences or new tumors, whichever you want to call them, have been in such patients.

Since technique was mentioned, and since Dr. Leadbetter described one technique and Dr. Spence said his was easier, I'll say mine is still easier. We make a Young-type perineal incision with a small vertical extension, not splitting the scrotum, just down the posterior scrotal wall. Through this the penis can be drawn down and the urethra dissected out at least up to the glans without making any anterior scrotal incision or any incision along the ventral surface of the penile shaft itself.

With regard to the detection of these recurrences, one technique that we have found fruitful when all others have failed has been the urinary cytology. As a matter of fact, we have inaugurated a followup system in all of our patients with cystectomy such that they get urethral washings made periodically during their followup visits to detect these recurrences earlier than might otherwise become clinically evident.

In the latter regard, I think I am quoting Mr. David Wallace of London correctly when I say that he found a 25 per cent incidence of in situ carcinomas in the urethras of patients dying following cystectomy in whom autopsy studies were carried out. I think that figure is correct. I think maybe Dr. Goodwin can verify that. Is that right?

DR. WILLARD GOODWIN (Los Angeles, Cal.): That's right.

DR. SCOTT: There was one other comment I wanted to make. With regard to the cobalt radiation, about two and a half years ago, we inaugurated a program of cobalt therapy in conjunction with cystectomy. This program was initiated by virtue of our dissatisfaction with the results of cystectomy alone in the treatment of bladder cancer.

At that time we had about a 10 per cent 5 year survival following cystectomy alone for patients with stage C lesions and about 16 per cent, I believe, for patients with B_2 lesions. For patients with OAB_1 lesions, the survival rate was about 45 per cent.

It is obviously too early to tell what this program has accomplished, but I think that you would be interested in a brief outline of what it has consisted. We examine our patients in a routine fashion by bimanual examination, cystoendoscopy, and transurethral biopsy under anesthesia. If they are considered candidates for cystectomy, they are dismissed from the hospital and given four weeks of cobalt irradiation, a total tissue dose to the bladder of about 4,000 r a week, as Dr. Taylor indicated. Then they are not cystoscoped until four to six weeks following completion of radiation therapy.

In about fifty patients—and my figures are approximate because we have not analyzed this material in detail—therapy has been in general well tolerated. Mind you, we go only to a tissue dose of 4,000 r. We have not had any disastrous complications from this dose.

About ten per cent of the patients have had complete cystoscopic disappearance of the tumor. Furthermore, at the time of the cystectomy, which we have in general routinely performed, in this group these 5 patients had no pathological evidence of tumor in their bladder at the time of cystectomy either.

I might say that that amount of radiation has not added any appreciable complication to the surgical problems. I think the vesical space heals a little more slowly.

Dr. Donald F. McDonald (Rochester, N.Y.): I would like to berate Dr. Cordonnier for being so incomplete in his radicalness for carcinoma of the transitional urethral lined spaces. He has forgotten completely about the ureters and the pelvis of the kidney. It has been well shown by experimental studies that it's just a question of time before the ureters and pelvis of the kidney can form tumors. I think we ought to reconsider the whole situation and start at the top and finish at the bottom.

The paper by my namesake certainly was a most interesting one that I enjoyed very considerably. The incidence of squamous-appearing lesions suggests that possibly the 2-AAF has a little different mechanism of action compared with betanaphthylamine. I wonder whether he has considered whether the vitamin B complex or A might be instrumental in the production of these tumors in the bladders of his rats on these depleting diets.

I wonder also whether he noticed any lesions of the urethra. I would be interested in his comment on this.

Dr. John K. Lattimer (New York, N. Y.): I can tell you briefly that Dr. Millikan has taken all of our bladder cancer patients for the last 2 years, analyzed their urine for beta glucuronidase, and found no correlation between the incidence of bladder cancer and the levels of beta glucuronidase in the urine. This is apropos of this one point.

Secondly, along the same lines of radiation therapy, using the betatron, we have had similar results as with the cobalt in that very few—actually, one out of some two hundred cases has had a complete disappearance with a two- or three-year failure of recurrence. That is all. We are using the betatron, the 24 million volt machine in place of cobalt. The results are similar.

Dr. Frank C. Hamm (Brooklyn, N. Y.): I would just like to say a word or two about the beta glucuronidase. From some preliminary observations that we have made in our laboratory, the excessive amount appearing in the urine in cases of cancer of the bladder may actually be effect and not cause. For example, we have compared the beta glucuronidase content in the bladder urine in contrast to that collected from the kidneys. There is a great discrepancy. The bladder urine contains a great deal more beta glucuronidase than does the kidney urine.

Furthermore, we think that it may be the product of the tumor. Actually, the tumor is rich in beta glucuronidase. I won't belabor the subject any further, but that is just a preliminary observation.

Dr. Thomas E. Gibson (San Francisco, Cal.): Years ago it used to be recommended in suprapubic excision of bladder tumors that the wound be lavaged after surgery was finished with pure grain alcohol or phenol. Three or four years ago, many of you will remember that Dr. Kiefer mentioned here that distilled water was cytotoxic for neoplastic cells. I would like to ask Dr. Weyrauch to comment on that.

I think that subsequently Dr. Frank Hinman, Jr. substantiated that statement by vital staining tests. I have been using distilled water. I can't say with what benefit, but I'd like to know if there's anything to that statement that can be presently supported. I know it was written up in the Urologic Correspondents Letter, too, by Dr. Kiefer. I would like to have Dr. Weyrauch's remarks.

Dr. John L. Emmett (Rochester, Minn.): I would just like to mention the observation regarding cobalt-60. It is possible to completely destroy the part of the bladder that contains the tumor with a necrotizing radiation dose of some sort and cure the tumor (using the word "cure" advisedly) and still have the patient fairly comfortable.

I recall two patients whom I saw recently. One was a young man, 44 years of age, who came 5 years ago after being treated at one of the veterans facilities for a year and a half for an extensive grade 3 carcinoma infiltrating in the lower half of the bladder, involving the right ureteral orifice and shutting off the kidney. On digital rectal examination there was very extensive metastasis. It felt almost like concrete poured down there. We resected and got down into perivesical fat. The tumor was in the perivesical fat.

I implanted a necrotizing dose of radon seed, about a millicurie and a half seeds, and too many for the area.

Three weeks later I took another biopsy. There

were still a few cells present of viable tumor. The patient was given cobalt therapy. Well, he had a terrible reaction for about three to six months. He was very uncomfortable. But after that, he has been comfortable. For 5 years he has been able to carry on his work. He is now 48 years of age. About every 6 months we have to go in there and pull out some of this encrusted material. There is no right lateral wall of the bladder. There is just a cavity there.

Another man whom I saw recently was taken care of by us 7 years ago. He had a lesion on the right wall of the bladder, which we considered hopeless. We put in a necrotizing dose of radon seeds and followed it with some deep x-ray therapy. For 2 years he had moderate symptoms and moderate difficulty. But he now is perfectly comfortable. He is retired and living in the California area, apparently cured of his tumor. He also has no right lateral wall of the bladder. It has completely disappeared.

Something to think about was mentioned here today. Maybe if this could be done in some of these hopeless cases; if you get too many symptoms afterward and then divert the urine, you might in some selected cases be able to cure the tumor or control it for many years.

QUESTION: What do you see when you look into it?

DR. EMMETT: Just a big hole, just a big cavity. At the bottom of it is a lot of mucus type of stuff. In some cases it gets pieces of encrustation on it. In this young man, you just reach in with a blunt forceps and pull a big hunk of it out. The reason he comes back to the clinic now is simply when he starts passing some of these chunks that are a little too big to come through the urethra.

In the other man, there is such a deformity of the bladder that it is difficult to look over into the area. The young man whom I was talking about will probably not die of his cancer. He is probably going to die of reflux of the remaining left ureter because the bladder has been so badly deformed now that he has vesicoureteral reflux.

I'm not suggesting that this is a good course of treatment, but I think those were two interesting observations of the possibilities of extreme irradiation.

MR. JACOBS (Glasgow, Scotland): With regard to Dr. Weyrauch's paper and his very interesting facts, I was reminded, when he was speaking, of the communication made by Franksson of Sweden in his monograph a few years ago in which he found that there was a higher incidence of recurrent bladder tumors in cases in which the resectoscope had been applied compared with those in which electrocoagulation had been carried out and the tumor dealt with through the cystoscope. That would seem to indicate that trauma is a factor predisposing to these new tumor formations.

I feel that if the instrumental manipulation is going to be very difficult, it is better to resort to open operation to deal with the tumor.

I would like, if I may, to show two slides. (Slide) This is a cystectomy specimen which I showed in November last at a clinical pathological meeting as an interesting specimen of a bladder with three large diverticula, one of which contained a massive infiltrative transitional cell carcinoma. A cystectomy and uretero-ileo-anastomosis were carried out. When I showed that specimen 3 months following the operation, I reported that the patient was well.

Three weeks later, that patient returned complaining of a swelling, a painful swelling, which was readily palpable in the perineum and some urethral bleeding. He had this tumor in the urethra, which was dealt with by urethrectomy. (Slide) You will notice that there is a considerable piece of urethra between the tumor and the bladder, and the original bladder tumor was in the diverticulum. There could be no possibility in this case of a spread. It again raises the question of whether this is a tumor resulting from spilling or due to a multifocal origin.

PRESIDENT RUSCHE: I would like to ask Dr. Weyrauch to close his paper.

DR. WEYRAUCH: First, in answer to Dr. Gibson's question, distilled water is not cytotoxic. We need something extremely more powerful than distilled water. In these experiments, distilled water was used to irrigate a wound after injecting numerous acetic tumorous cells. In rats we get 100 per cent take. This is Dr. Warren Cole.

We can even reason it out on our own theoretical basis. Say we had ten cells together instead of one. Even if distilled water were cytotoxic, it certainly wouldn't be powerful enough. It would be diluted down around the periphery and wouldn't get to the inner cells.

I think with all the discussion today that we have all agreed on one thing, that our present

measures in treating cancer of the bladder are inadequate. It has been very interesting that we all agree on that.

It seems to me that with radical surgery we are not going to get the final answer. Even if you take out all the kidneys, the ureters, and the urethras, we still don't get the final answer. Perhaps we should take a leaf from our book in treating prostatic cancer. Even though that is not as malignant a tumor, we have learned that our theory of multiple attack has been valuable. We use estrogens; we use hormonal therapy; we use chemotherapy; we use x-ray.

I think that in addition to surgery, we need something in addition in cancer of the bladder. Dr. Scott mentioned using methods of prophylaxis. I think that is ideal. I think chemotherapy may prevent recurrence. We should go into chemotherapy to cover the patient during operation. Maybe that would be just as effective in preventing these urethral occurrences as would be taking out the urethra, even though we leave the penis behind.

With respect to supervoltage radiation therapy, I think the cobalt blues are somewhat over-rated in Baltimore. Out in the salubrious sunshine of the West with our linear accelerator, we find that patients don't get cobalt blues. We have used up to 7,000 r and are getting much fewer reactions than we described here today. The answer is to spread the treatment out over a longer period of time. Don't pile it all in at once. Use rotation. Use multiple quartz.

I think that we may even cure patients with x-ray. I am sure that in a few of our series—we have done something like 80, not 5-year cures yet; but some of them, I am sure, were cured who could not have been cured by surgery. Dr. Whitmore, I think, believes that, too. I think that is part of our theory of multiple attack.

One question which has never been answered, I think we have to go to the laboratory for a solution; we have to wait 5 years for our clinical experiences. It would be interesting to meet here in Las Vegas 5 years hence and learn where we are then. But one question that we should answer is whether radiation therapy grants any immunity to recurrence. I have talked to radiologists and urologists, and nobody has ever been able to answer that question. Some day I hope we can get to the laboratory and find it. If somebody does know the answer, will he please take it up in his final remarks?

PRESIDENT RUSCHE: We'll ask Dr. Cordonnier to close his paper.

DR. CORDONNIER: I just want to read the title to the manuscript for Dr. Spence. I did make one mistake. I said Urethral Recurrence of Bladder Carcinoma following Cystectomy. It should be Urethral Occurrence. That was corrected.

As far as Dr. McDonald's quasi-facetious remarks, we all know that people with bladder cancer are apt to have papillary tumors of the renal pelvis. Melicow has certainly emphasized that through the years.

On the other hand, I have not been impressed with the incidence of recurrence following bladder cancer in individuals in the upper tract as much as I have below. In other words, I am quite sure that the urethral recurrence has been far greater than that in the upper urinary tract. It is true that one or two of these patients have developed upper tract lesions, but they have not been outstandingly so.

PRESIDENT RUSCHE: Dr. McDonald!

DR. MCDONALD: Dr. Leadbetter was wondering about the work being done as to metabolites of 2-AAF. We do know—not from our own work, but from previous work—that 2-AAF is deacetylated in the liver. It is hydroxylated, and it is conjugated. The bulk of it is excreted as a conjugate in the urine.

We are at the present time in a program in the use of chromography and isotope studies in an attempt to delineate the metabolites which occur and which might be different in those animals which develop tumors in the presence of benign cystadenomas on the liver and in those animals which develop tumors in the presence of the hepatic malignant tumors.

Dr. Scott mentioned that they did not get bladder tumors in their animals without the use of indole. As you will recall, we did have six papillomas of the bladder at about the age of 6 months in our rats which received 2-AAF without the indole. The presumed reason we did not get carcinoma was that these animals died very shortly thereafter.

With regard to Dr. McDonald's comments on the squamous cell carcinomas which we secured, these animals did receive, we felt at least, ade-

quate vitamin supplementation. As such, we cannot at the present time pinpoint that as a reason for squamous cell development. We saw no lesions of the urethra that we know of.

I might add one thing to Dr. Weyrauch's paper. We are now in the process of a study which is supplementary to the one given by the beautiful Swedish girl at the 1960 American Urological Association* meeting in which we are using nitrogen mustard prior to operation and diverting the operative procedure and running the usual vena cava blood specimens for the presence of circulating tumor cells. In a very, very preliminary review of results, we are finding that the nitrogen mustard does nothing as far as increasing the incidence of circulating tumor cells.

PRESIDENT RUSCHE: Dr. Taylor, would you like to close?

DR. TAYLOR: I would just like to say that I agree with Dr. Weyrauch that our present treatment of bladder cancer leaves a lot to be desired. I think we should never cease trying for modalities until we conquer it.

* J. Urol., **85**: 1–12, 1961.

PARARENAL PSEUDOCYSTS: A REPORT OF FOUR CASES

CARL L. SAULS AND REED M. NESBIT

The classical physical findings as well as the dire consequences of extravasated urine are well known to the surgeon. That retroperitoneal urinary efflux, under certain circumstances, may remain difficult to detect and cause significant renal damage is less well appreciated. The purpose of this report is to focus attention on the clinical setting of this pathologic process, and present four such cases, three following urologic operations, that have been encountered recently.

Pseudocysts in the region of the kidney occur as a result of trauma, either accidental or operative. The lesion may be slowly progressive and is usually associated with hydronephrosis. Although a cystic lesion, there is no epithelial lining within the space. Destruction of the kidney may be the ultimate result of the process as shown by both clinical and experimental studies.

CASE REPORTS

Case 1. J. L., a 37-year-old auto mechanic, sustained multiple injuries in an automobile accident when he was hurled through the windshield. His injuries included fractures of the pubic rami and left hemisacrum, subluxation of the left sacroiliac joint, and facial lacerations. There was disruption of the membranous urethra; continuity was reestablished by an indwelling balloon catheter that was placed on traction for 13 days and removed prior to his discharge from the hospital. He was essentially asymptomatic except for intermittent, mild, left abdominal aching discomfort at the time he returned home. Following his hospital discharge, the discomfort in the left side of the abdomen became progressively more severe; the pain began to radiate to the left testis and pain in the left flank appeared. After a period of time at home, he sought medical advice at the Veterans Administration Hospital in Ann Arbor concerning his symptoms; this was 5 weeks following the accident.

Physical examination revealed a large, firm, non-tender mass filling the left side of the abdomen and left flank. There was no costovertebral angle tenderness, and bowel sounds were present. The remainder of the physical examination was not remarkable.

The hemoglobin was 12.5 gm. and the white blood count 12,500. The urine was cloudy yellow with a specific gravity of 1.032, 1 plus albumin and no glucose. Spun sediment of the urine revealed 3 to 5 red blood cells, many white blood cells, but no casts. Many cocci were apparent on the stained urinary sediment.

Intravenous urograms were obtained (fig. 1). The right pyelogram appeared normal. On the left, the psoas shadow was obscured by a large, soft tissue mass and there was delayed appearance of the contrast medium in the left renal collecting system. This kidney was displaced superiorly with the inferior pole pushed laterally so that an almost horizontal position had been assumed by the organ. Slight hydronephrosis was present. The left ureter was not visible.

Aspiration of the mass through the flank using an 18 gauge needle recovered turbid, straw colored fluid. Culture of this fluid failed to produce any bacterial growth.

Prior to operative exploration, a left retrograde pyelogram was obtained. The catheter became arrested within the upper third of the ureter and injection of contrast medium opacified the retroperitoneal mass. The ureteral catheter was left indwelling and the patient moved to the operating room.

The retroperitoneal space was entered through the bed of the twelfth rib exposing a large cystic mass extending to below the iliac crest. This was opened and 2500 ml. cloudy yellow fluid removed. Fatty and oily debris was scattered throughout the contents. Inspection of the cavity revealed several tiny holes in the mid-ureter communicating with the inferior portion of the pseudocyst. No connection of the ureter with the renal pelvis could be found as this former structure was imbedded in dense fibrous tissue along the medial wall of the cavity. The roof of the pseudocyst was separated from the renal parenchyma by a layer of granulomatous appearing tissue. A nephrectomy was performed and the retroperitoneal space drained. The patient's postoperative course was uneventful and he was discharged on the fifteenth postoperative day.

Microscopic examination of the pseudocyst

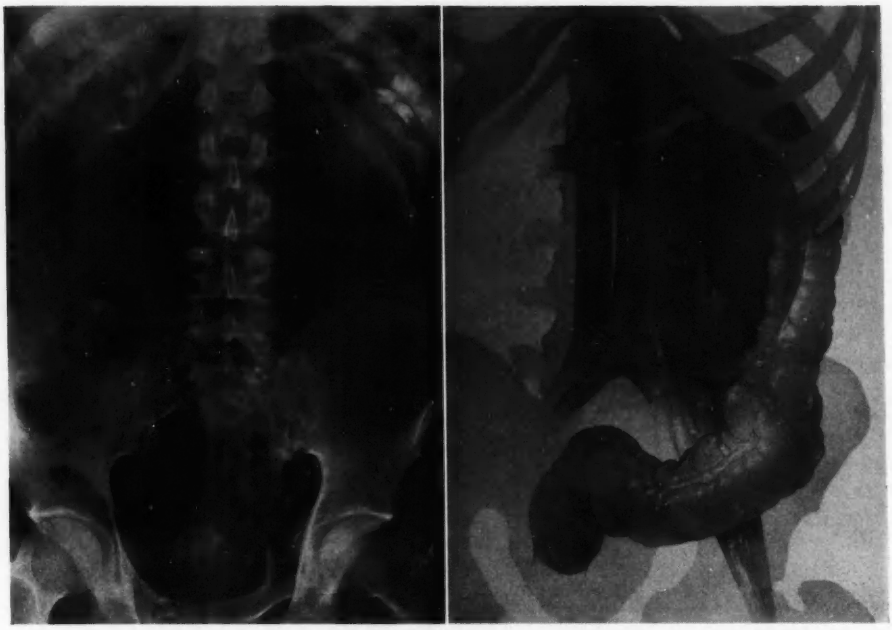


FIG. 1. Case 1. Intravenous urogram shows displacement of left kidney and obscuration of left psoas shadow. Drawing depicts location of pseudocyst; "window" reveals posterior pseudocyst wall in cross-section.

wall revealed recent focal hemorrhages, hyalinizing scar tissue extending into fat, and focal aggregates of chronic inflammatory cells. Active fibroblastic and angioblastic proliferation was also present. There was no epithelial lining within the sac.

Case 2. L. H., a 20-year-old college student, underwent a pyeloplasty of the right kidney following a preoperative evaluation that had uncovered an obstruction of the right ureteropelvic junction secondary to a fibrous band and a high insertion of the ureter into the renal pelvis. The postoperative course in the hospital was uncomplicated. The Penrose drain that had been placed at the pyeloplasty site was removed on the seventh postoperative day; urinary drainage from the operative repair had been minimal throughout the immediate postoperative period and there was no drainage at the time the drain was removed. He was asymptomatic at the time of hospital discharge on the eighth postoperative day.

Following his return home the patient remained free of symptoms. Intravenous urograms, made 3 months following operation as a followup examination, revealed an increased degree of hydronephrosis as compared to the preoperative films (fig. 2). Checkup examination 6 months postoperatively uncovered a non-tender mass in the right flank; intravenous urograms failed to opacify the right kidney. The patient was then readmitted to the hospital.

Physical examination was not remarkable except for a non-tender mass filling the right flank, extending inferioriy to the iliac crest and anteriorly to the mid-clavicular line. The hemoglobin was 16.8 gm., the white blood count 6,600 and the urine negative. Twenty-five per cent excretion of phenolsulfonphthalein occurred in 15 minutes. The blood urea nitrogen was 15 mg. per cent.

An operative exploration of the right kidney was performed on the morning following his admission. Upon entering the retroperitoneal space, a cystic mass was encountered and opened. A collection of turbid, straw colored fluid was found within a sac that communicated with and surrounded the ureteropelvic junction. The inferior portion of the renal pelvis and upper 3 cm. of the

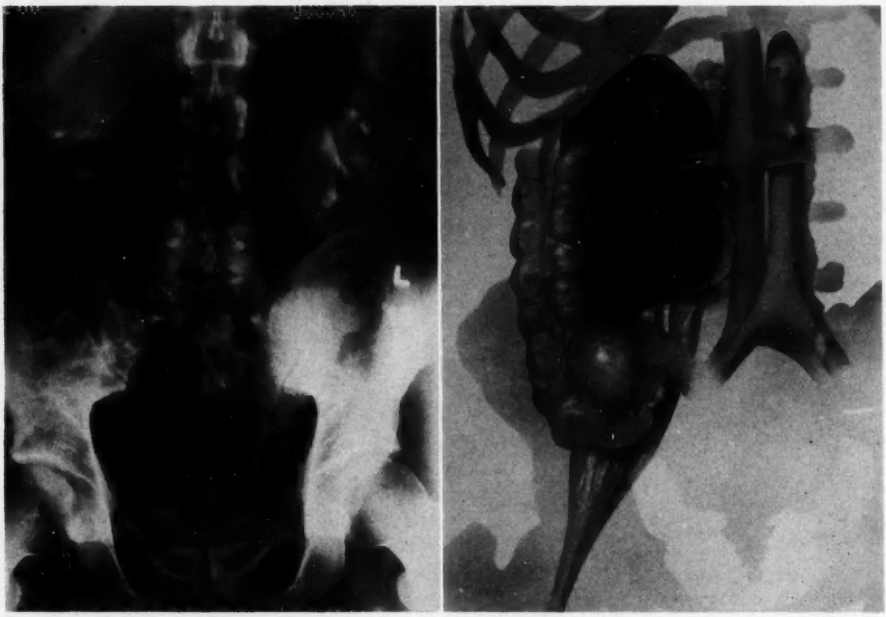


FIG. 2. Case 2. Intravenous urogram reveals significant right hydronephrosis 3 months prior to second operation. Note in illustration how pseudocyst surrounds and compresses ureteropelvic junction like a collar.

ureter were within the space and firmly fixed at the inferior and superior extent of the pseudocyst by fibrosis. The renal pelvis was opened and marked hydronephrotic atrophy of the kidney confirmed. A nephrectomy was performed. The postoperative course was uncomplicated, and the patient has remained in good health.

Microscopic examination of the pseudocyst wall showed dense fibrous tissue with active chronic inflammation in continuity with bundles of skeletal muscle. The sac wall was bare of epithelium. The renal parenchyma not only revealed hydronephrotic atrophy but also a chronic inflammatory infiltrate within the interstitial tissue.

Case 3. K. C., a 57-year-old carpenter, had a right pyelolithotomy during which the calculus was removed from the renal pelvis through a 1 cm. pyelotomy incision. This opening was closed with size 5-0 chromic catgut interrupted sutures and a Penrose drain left in place. The immediate postoperative course was uncomplicated. The drain was removed on the seventh postoperative day; there was no urinary drainage at that time. He was discharged on the eighth day following operation.

The patient returned 2 years later. He had been free of symptoms following his operation for 22 months. He had then begun to notice intermittent right flank discomfort. This had become particularly bothersome at night and interfered with his sleep. Physical examination revealed mild tenderness to deep palpation in the right upper quadrant of the abdomen but was otherwise not remarkable. The hemoglobin was 15.2 gm., white blood count 7,900, and examination of the urine was negative. The blood urea nitrogen was 17 mg. per cent. The left kidney appeared normal but the right failed to visualize on excretory pyelograms. Right hydronephrosis was apparent on a retrograde pyelogram and 50 cc of urine was found in the renal pelvis (fig. 3). The patient's symptoms were relieved following the retrograde catheterization.

The patient was readmitted to the hospital and a right renal exploration performed. A large cystic mass was immediately encountered upon entering the retroperitoneal space. This structure

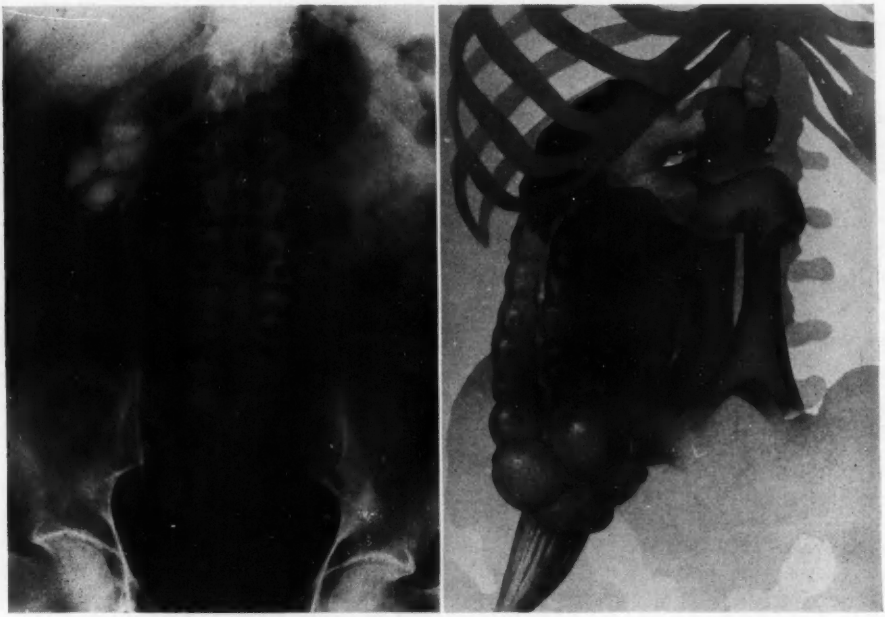


FIG. 3. Case 3. Right retrograde pyelogram demonstrates hydronephrosis and ureteral tortuosity at superior margin of pseudocyst. Retroperitoneal cystic space extends posterior to ascending colon, as illustrated.

was entered and approximately 1000 cc clear amber fluid removed; culture of this fluid was negative. The sac wall was smooth and glistening. Further dissection uncovered the ureter in the medial wall of the pseudocyst where it was firmly bound down in dense scar tissue. The upper ureter crossed the space like a tight rope as it passed laterally and superiorly to enter the renal pelvis. Cicatrization was particularly dense in this upper portion. No communication between the pelvis or ureter and the pseudocyst could be identified. Ureterolysis was accomplished and followed by establishment of an intubated ureterotomy utilizing a red rubber T-tube.

Microscopic examination of the cyst wall showed it to be composed of fibrous connective tissue with areas of hyalinization and minimal focal calcification. Aggregates of chronic inflammatory cells were also present. There was no epithelial lining present.

The patient's early postoperative course was marred by low grade fever associated with wound infection. The T-tube drained up to 200 cc per 24 hours but this volume gradually diminished; the tube was then clamped and this maneuver was well tolerated. The patient was discharged from the hospital with the clamped T-tube in place. The intubating catheter was removed 6 weeks following operation.

Followup excretory urograms have continued to show non-visualization of the right kidney, but a postoperative retrograde pyelogram taken 3 months following operation has confirmed a definite decrease in the degree of hydronephrosis. The patient has remained clinically well.

Case 4. L.S., a 44-year-old drug salesman, underwent a ureterolithotomy for an impacted calculus in the left upper ureter. Following discharge from the hospital, after an uneventful recovery, the patient began to have aching discomfort in the left flank. Intravenous urograms, taken 1 month after operation, revealed extravasation of the contrast medium into the retroperitoneal space in the region of the ureterotomy site. Open surgical drainage of this area was accomplished with the removal of approximately two liters of urine. Urinary

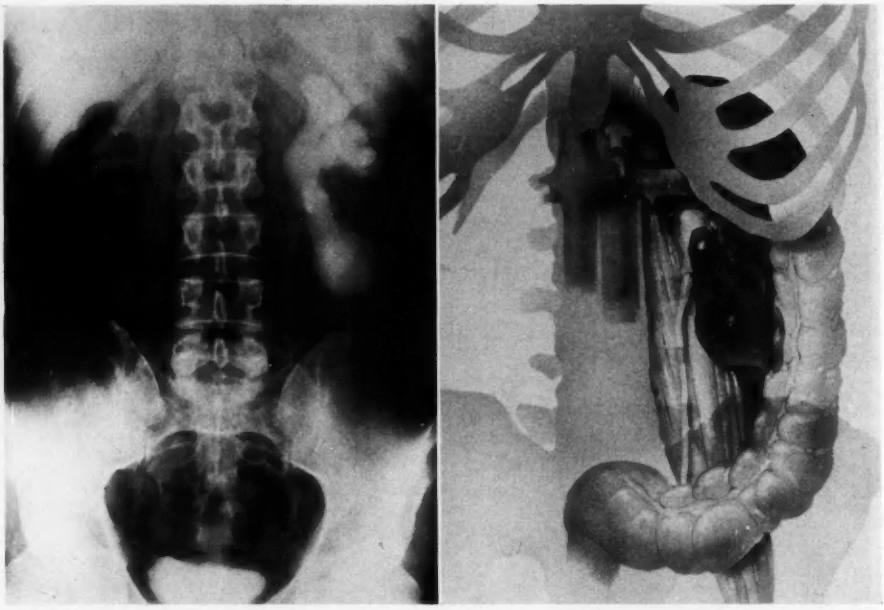


FIG. 4. Case 4. Intravenous urogram shows prompt efflux of contrast medium into juxtaureteral space. Illustration accurately depicts psoas muscle comprising portion of posterior wall of pseudocyst.

drainage from the wound persisted for 3 weeks, then subsided.

He was referred to the University of Michigan Medical Center 2 days after the drainage had ceased. The patient was asymptomatic and afebrile. Intravenous urograms revealed left hydronephrosis as well as prompt spill of the contrast medium into a pararenal space (fig. 4).

Physical examination revealed a well healed flank incision with no drainage occurring through a 2 mm. open drain site. There was no flank or abdominal tenderness. The hemoglobin was 12.8 gm., the white blood count 6,650. Examination of the urine showed a trace of albumin and no glucose; the spun sediment revealed 10–15 white blood cells and 10–15 red blood cells and bacilli. Culture of the urine proved the organisms to be Proteus mirabilis. The serum creatinine was 0.8 mg. per cent, serum calcium 10.1 mg. per cent, and the serum phosphorus 2.9 mg. per cent.

A left retroperitoneal exploration was performed; the surgical approach was made inferior to the pseudocyst and the ureter was then identified. The ureter was traced superiorly and was found to be firmly fixed in dense scar tissue approximately 5 cm. below the ureteropelvic junction. Continued dissection resulted in the opening of a juxtaureteral space. The posterior wall of this space was formed by the psoas muscle and a definite sac wall had not yet developed. Culture of the area yielded no growth. The ureter was dissected free and a small opening found near the ureteropelvic junction. After complete ureterolysis in this area and after ascertaining the presence of a patent ureter by passing a probe both superiorly and inferiorly, the operation was completed by placing a Penrose drain at the point of leakage and closing the wound.

The postoperative course was uncomplicated until the tenth day when the patient's temperature was 103F. There were no localizing signs; the white blood count was 7,100 with no shift to the left. Blood cultures were negative but the urine was found to be infected. The fever fell by crisis 6 days following its onset and 2 days following treatment with antimicrobial drugs.

Intravenous urograms 3 weeks following operation showed moderate left hydronephrosis as well as definite extravasation of contrast

medium in the region of the upper ureter. A ureteral catheter was passed to the renal pelvis and left indwelling for 6 days, but a retrograde ureterogram obtained at the time of its removal continued to show the ureteral leak, and re-establishment of ureteral intubation was necessitated. Again, after 12 days, the ureteral catheter was removed; the patient then remained asymptomatic and afebrile. Intravenous urograms continued to confirm the presence of mild left hydronephrosis but no effusion of contrast medium could be seen.

The patient has remained clinically well. Continued mild hydronephrosis was apparent on the most recent excretory pyelograms taken 2½ months following operation, but there was no evidence of extravasation.

DISCUSSION

Encysted collections of fluid that surround or are in juxtaposition with the kidney occur infrequently. These lesions have aroused the curiosity of clinician and pathologist alike concerning their etiology and significance; however, controversy continues. Spriggs[1] reviewed the problem thoroughly and chose to classify such cystic structures under three general headings: 1) perinephric extravasation, 2) perinephric hematoma, 3) perinephric cyst of doubtful origin. The difficulty of identifying any given lesion as to its origin is obvious, but it would appear that the cases just presented would fall into Sprigg's first group.

A review of available literature reveals that no individual surgeon has had the benefit of observing more than a few cases of pseudocyst formation following urinary extravasation. The largest series previously reported consists of only 3 cases; the majority of reports are of solitary cases. The lesion has been noted in infants as well as adults.[2, 3] Unfortunately, there has been no uniformity of nomenclature, and this has maintained a certain amount of confusion concerning the entity; pseudohydronephrosis,[4] perirenal cyst,[5] perinephric cyst,[1] and hydrocele renalis[6] are some of the terms encountered in a perusal of the case reports. The title of this paper was chosen by the authors because it is descriptive of the pathologic process.

Hawkins,[7] a British practitioner, first reported this clinical entity in 1834. He ministered to a child who had been run over by a wagon. A mass in the flank made its appearance on the tenth day following the traumatic episode. The injuries were ultimately fatal and a postmortem examination disclosed two small holes in the renal pelvis and a large retroperitoneal collection of urine. Over a hundred years later, Crabtree[4] reported 3 cases, and his treatise aided greatly in pinpointing the condition as a definite entity as well as clarifying the probable pathogenesis. He was able to cull but 20 cases from the literature at that time. The underlying etiology has been accidental trauma with few exceptions. Block[8] recorded 1 case that resulted from perforation of the renal pelvis by a calculus. Pyrah and Smiddy[9] observed the only previous case to be reported as a postoperative complication; they encountered the lesion following a pyelolithotomy upon a kidney having an intrarenal pelvis and commented that the ureter was almost completely avulsed from the renal pelvis during the operative manipulation thus necessitating a difficult repair of the collecting system. The chain of events that occurred during the postoperative period is very similar to our case 4. Several cases have been noted to follow the traumatic avulsion of the ureter from the renal pelvis, and this may have been the etiology in our first patient who had sustained multiple injuries in an automobile accident. Hyman[10] encountered a periureteropelvic cystic structure in a patient undergoing celiotomy for what was thought to be an acute abdomen. The patient had had the acute onset of severe right upper quadrant abdominal pain and the diagnosis was in doubt at the time of the operative intervention. No history of trauma is mentioned, and microscopic examination of the cyst wall suggested the presence of smooth muscle fibers. The author advanced the hypothesis that the process may have represented a urinary dissection of the ureteral wall. Special staining techniques in our cases have revealed

[1] Spriggs, A. I.: J. Urol., **67:** 414, 1952.
[2] Poutler, E. E. and Garvey, F. K.: J. Urol., **70:** 840, 1953.
[3] Sturdy, D. E. and Magell, J.: Brit. J. Surg., **48:** 315, 1960.
[4] Crabtree, E. G.: Trans. Am. Assn. Genito-Urin. Surg., **28:** 9, 1935.
[5] Johnson, C. M. and Smith, D. R.: J. Urol., **45:** 152, 1941.
[6] Mulholland, S. W.: J. Urol., **41:** 653, 1939.
[7] Hawkins, quoted by Crabtree.
[8] Block, quoted by Crabtree.
[9] Pyrah, L. N. and Smiddy, F. G.: Brit. J. Urol., **25:** 239, 1953.
[10] Hyman, J.: J. Urol., **70:** 32, 1953.

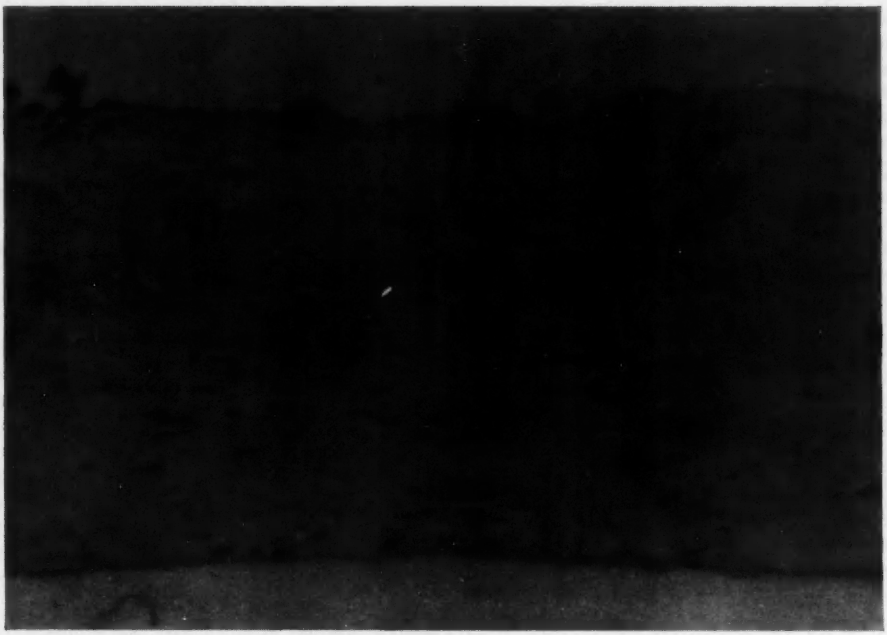


FIG. 5. Photomicrograph of pseudocyst wall. Structure is composed of dense fibrous tissue; no epithelial lining.

only fibrous tissue to be present (fig. 5). The latent period between the traumatic episode and the appearance of symptoms may be as long as 2 years; such was the situation in our case 3. Johnson and Smith[5] reported a patient found to have a markedly calcified pseudocyst associated with a non-functioning kidney. Their patient had no symptoms and the mass was found on a routine physical examination. Upon interrogation, she was able to remember a traumatic occurrence in her childhood that had required confinement to bed; the interval in her case had been 37 years. This particular example would seem to indicate that the pathologic process occasionally reaches completion without significant symptoms.

Certain experimental work relating to this problem is significant. Delbet,[11] working in 1903, was unable to produce the lesion in the laboratory. He proved in the rabbit that laceration or section of the renal parenchyma did not cause excretion of urine on the cut surface. After section of the pelvis or ureter by a long slit, a small infiltration of urine took place but was promptly resorbed. He produced a hematoma at the same time of the extravasation but found that the former was also readily resorbed. He was misled into thinking that secondary infection played a vital role in the development of the cystic lesion. In 1922, Razzaboni[12] produced the condition with regularity by severing the ureter near the kidney and reapproximating the perirenal tissues. Examination of his experimental animals at intervals varying from 24 hours to 62 days was then performed. He found that between 24 and 48 hours there was no sac wall; at this time the urine was actively infiltrating the pararenal tissues. A characteristic effect upon the fat cells caused by the urine was rapid lipolysis. The lipolysis was almost complete at 5 days and active fibroblastic proliferation was noted. A definite sac wall was found by 12 days with continued chronic inflammatory changes as well as proliferation of fibrous tissue. By 20 to 40 days, the fibrous tissue of the sac wall had matured to dense connective tissue. In the one

[11] Delbet, quoted by Crabtree.

[12] Razzaboni, G.: Arch. ital. Chir., **6**: 365, 1922.

animal that survived 62 days, there was little further change except for condensation and cicatrization of the sac wall. Microscopic examination of the renal parenchyma revealed progressive tubular dilatation and atrophy as well as fibrous proliferation in the interstitial tissues.

COMMENT

A study of the clinical and experimental knowledge available leads one to suspect that certain rigid criteria must be fulfilled for a pseudocyst to result from a retroperitoneal urinary effusion. Undoubtedly, the usual fate of urine that spills into the tissues about an operative site is resorption. If pocketing of urine occurs following an operation, the common sequel is the onset of sepsis due to associated infection. This latter complication necessitates prompt surgical drainage. Following accidental trauma, the onset of fever often heralds the presence of urinary extravasation, and operative intervention ensues; such a case is well described by Crosby.[13] It would thus appear that for such a retroperitoneal leak to remain undetected, the urinary efflux must be sterile and remain so. As pointed out by Crabtree, the type of injury is important. The collecting system of the kidney must be opened or secreting fragments of kidney tissue separated from the main renal mass. Following the injury, persistent efflux of urine into the surrounding tissues must take place. This latter process may be engendered by a transient distal obstruction such as an intraluminal blood clot within the ureter or a periureteral hematoma. After a period of time, tissue reaction in the region of the defect probably results in a continuing element of obstruction. A vicious cycle would then be present (fig. 6). The rate of intumescence of the false cyst would not only depend upon the percentage of urinary output that finds its way into the retroperitoneal space but also upon the rate of urine formation. This hydrokinetic system would then reach stability only when autonephrectomy occurs. If this accurately depicts the process, it is not surprising that an obvious communication with the collecting system is difficult or impossible to identify in those lesions that appear clinically long after the injury. Although autonephrectomy may occur before symptoms are significant, as represented by the case of Johnson and Smith, the onset of pain usually seems to intervene.

[13] Crosby, D. L.: Brit. J. Urol., **31**: 159, 1959.

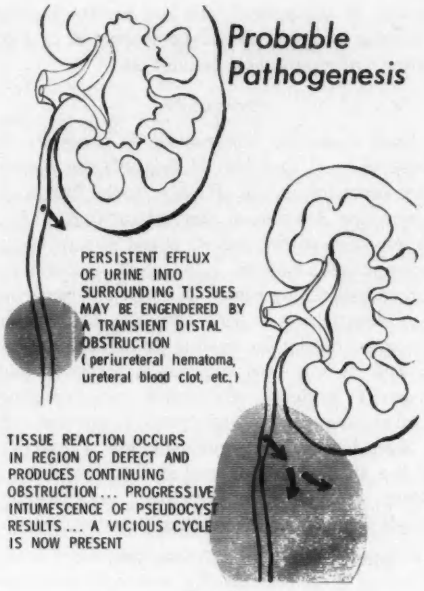

Probable Pathogenesis
PERSISTENT EFFLUX OF URINE INTO SURROUNDING TISSUES MAY BE ENGENDERED BY A TRANSIENT DISTAL OBSTRUCTION (periureteral hematoma, ureteral blood clot, etc.)
TISSUE REACTION OCCURS IN REGION OF DEFECT AND PRODUCES CONTINUING OBSTRUCTION ... PROGRESSIVE INTUMESCENCE OF PSEUDOCYST RESULTS ... A VICIOUS CYCLE IS NOW PRESENT

FIG. 6

DIAGNOSIS

If the entity is kept in mind, the diagnosis should not be difficult in the usual case. A history of trauma or prior operation upon the kidney or upper ureter associated with a mass in the flank should lead one to quickly suspect the underlying process. It is important, however, to make the diagnosis early so that operative correction can be performed before irreparable damage has occurred to the kidney. In the early stages of the disease, establishment of the diagnosis remains a challenge. The patient may be free of symptoms and the urine is often normal. Excretory pyelography is helpful. Although actual opacification of the cyst may occur very early in the process, the usual finding is hydronephrosis or non-visualization. If the pseudocyst is large, the kidney may be displaced and the psoas shadow obscured by a soft tissue density. At the time of cystoscopy, an absence of urinary efflux from the ureteral orifice on the affected side may be noted. Although an uncommon lesion, any patient who has progressive hydronephrosis following an operation upon the upper ureter or renal pelvis,

as well as the patient who has similar findings following trauma, should be suspected of harboring a retroperitoneal pseudocyst.

TREATMENT

Early operative intervention is necessary to preserve renal function. If delayed, the disease may cause irreparable damage to the kidney as in our case 2. Even if attacked early, operative preservation of the kidney is not always easily accomplished. Careful lysis of all periureteral fibrous tissue is necessary to remove all elements of obstruction; it is then advisable to intubate the ureter during the healing period. Reports[3, 14] as well as our own experience, indicate that recurrent ureteral obstruction or persistent extravasation is not infrequently encountered. If there has been a significant loss of function by the affected kidney and if the contralateral kidney is normal, nephrectomy is advisable. Simple drainage of the space appears inadequate and continued effusion can be expected if this procedure is followed. The one reported cure by drainage alone was followed for only 13 days.[15]

Although previously considered a rare disease, the ever rising frequency of traffic accidents and the widespread use of antimicrobial drugs may so engender the development of the pathologic process that the clinical problem may be more commonly encountered in the future.

SUMMARY

Four patients having pararenal pseudocysts are presented.

The disease is discussed and the probable pathogenesis commented upon.

The authors wish to acknowledge the help of Mr. Alfred Teoli of the Department of Medical Illustration, University of Michigan Medical School, for the illustrations depicting the in situ pathologic findings.

[14] Zufall, R.: J. Urol., **85**: 246, 1961.

[15] Stirling, W. C.: Med. Ann. Dist. Col., **3**: 41, 1934.

MULTILOCULAR CYST OF THE KIDNEY: CASE REPORT

THOMAS E. GIBSON

From the Department of Urology, St. Joseph's Hospital, San Francisco, Cal.

The nosology of renal cystic disease presents an amazing complexity with respect to etiology and pathogenesis. Abeshouse in 1950 enumerated some sixteen varieties of renal cysts. In 1955 Spence for the first time drew a sharp line of distinction between *polycystic disease, multilocular cysts and multicystic disease.* He reported 3 cases of multicystic disease and analyzed 15 cases reported in the literature. In 1960 Ivker and Keesal reported three more cases of multicystic disease and reviewed the literature to date. In 1956 Boggs and Kimmelstiel reported 2 cases of multilocular cysts of the kidney and found 14 cases in the literature meeting the rigid criteria established for this lesion.

The following case of a multilocular cyst of the kidney is reported because of its rarity and certain unusual features.

CASE REPORT

A woman aged 64 years, in good general health, except for moderate hypertension, reported to her physician for a routine checkup. During this examination a mass was detected in the region of the right kidney. Urological investigation revealed a normal left kidney, but a non-functioning right kidney, thought to be a neoplasm. Retrograde pyelography was unrevealing since no medium could be introduced into the kidney pelvis (fig. 1). A nephrectomy was performed. Convalescence was uneventful. On the tenth postoperative day, when the patient was ready to go home, she suddenly died, presumably from an embolus. No autopsy was obtained.

Because of the unusual nature of the specimen (fig. 2), the pathologist's report is presented in detail:

"Gross: The right kidney, fixed in formalin, weighs 340 gm. and measures 12.5 cm. from superior to inferior pole, 8.5 cm. from the hilus to the cortex and 6.5 cm. in the anterior posterior diameter. The kidney capsule strips with some difficulty leaving a bossellated, roughened, grayish white surface over the upper half of the kidney and a mottled yellowish grey and brown surface over the lower half of the kidney. Arising from the upper anterior portion of the kidney is an ill-defined multicystic, lobulated mass which measures approximately 9 cm. in diameter. The upper pole is well separated from this mass. The renal pelvis is relatively prominent and enlarged; its extrarenal portion measures 5 cm. in greatest diameter. A 6 cm. portion of ureter is attached to the specimen. The ureter measures 1.7 cm. at the ureteropelvic junction and gradually decreases in size to a diameter of 1 cm. at the line of resection. On coronal section of the specimen the following major alterations from the normal are observed. The kidney pelvis is markedly dilated. The mucosal surface is thickened, finely granular, gray-tan. It is intact and trabeculated in places. The superior calyx and infundibulum are easily identified and, except for moderate dilatation, present essentially negative findings. The middle calyx likewise is readily identified. It is greatly dilated and its wall is composed of a polycystic tumor mass. Projecting through the greatly dilated infundibulum is a pedunculated tumor presently to be described, which snugly fits into the pelvis. The inferior calyx and infundibulum are greatly dilated, but otherwise regular. Corresponding to the bosselated tumorous area noted in the gross, the kidney parenchyma in the anterior superior and midportion is replaced by a multicystic honeycombed tumor mass from which arises the pedunculated cystic tumor previously mentioned. This measures 8 by 6 by 3.5 cm. and arises from a relatively narrow base, measuring 2.5 cm. in its greatest diameter. It is staghorn-shaped, and its inferior lip fits snugly into the ureteropelvic junction. The cystic masses vary in size from pinpoint to 3 cm. in diameter. They are filled with a clear fluid; their inner lining is smooth. The cyst walls are thin with very little intervening parenchyma and are composed of dense, grey, fibrous tissue. The kidney parenchyma of the superior pole, of the posterior aspect as well as the inferior third of the kidney, including the inferior pole, shows similar findings. The corticomedullary markings are obliterated. The kidney parenchyma is replaced by a rather uniform, firm, tan tissue which measures approximately 1 cm. in thickness.

"The ureter is slightly thickened. Its mucosal

FIG. 1. Attempted right retrograde pyelogram unsuccessful because renal pelvis tightly distended by bulging cystic mass in kidney. (Photographer reversed x-ray in process of making print. Editor.)

lining is intact, uniform, grey-tan and finely granular. The renal vessels are transected close to the hilus and show no gross abnormalities. The peripelvic fat is moderately increased in amount and is indurated.

"Microscopic: Sections 1, 2, and 3 taken from the superior and inferior poles show thickened capsule. The renal parenchyma is largely replaced by fibrous tissue which is heavily infiltrated with predominantly lymphocytes [fig. 3]. The infiltrate occurs in focal, in places streaky, fashion. Aggregates of dilated and atrophic convoluted tubules are scattered through the cortex; some tubules are filled with eosin-staining colloid material. The glomeruli show considerable alteration, varying from fibrous thickening of capsule, through various stages of fibrosis of glomerular tuft, to complete hyalinization of the glomerulus. Vascular channels also show definite alterations; the arteries present moderate to marked proliferative endarteritis; the arterioles

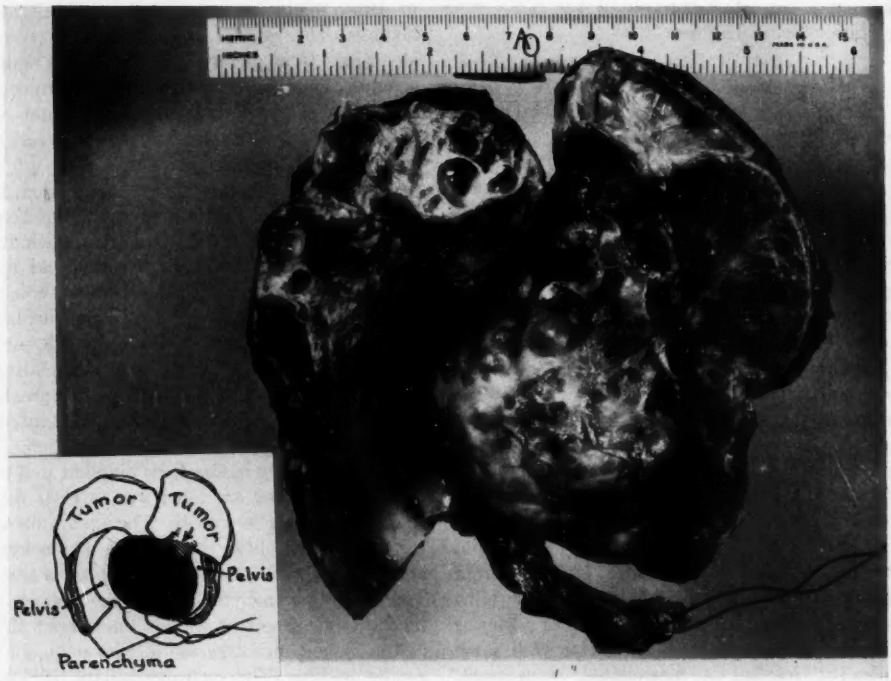


FIG. 2. Kidney after longitudinal section reveals cystic structure with large, pedunculated cystic mass distending renal pelvis. Entire upper part of kidney is cystic, but lower pole shows remnant of parenchyma thinned out by pressure atrophy.

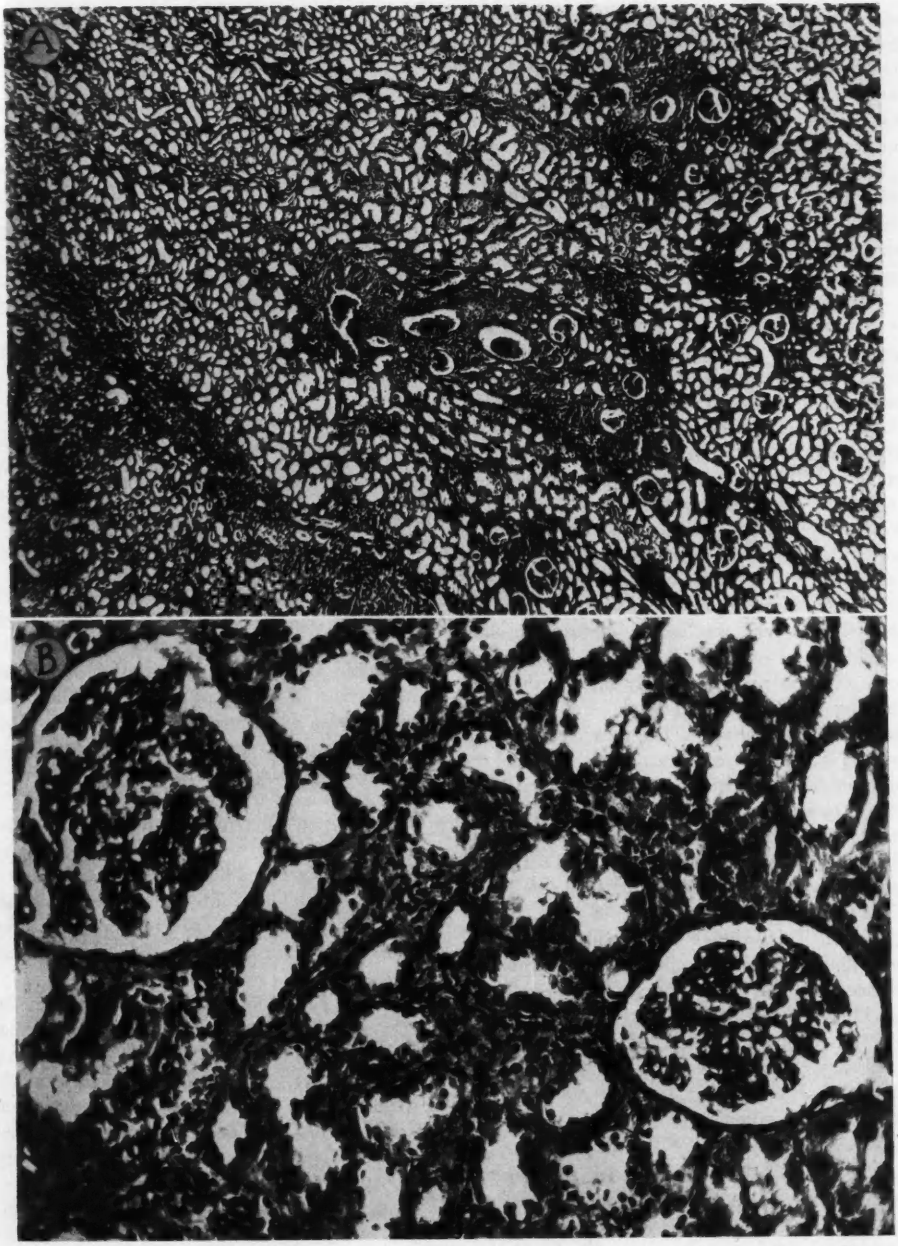


FIG. 3. Low (*A*) and high (*B*) power photomicrographs of adjacent renal parenchyma. Pressure atrophy with dilatation of tubules and chronic inflammatory changes are obvious.

show endothelial proliferation, in some marked hyaline thickening of the wall. Most arterial channels consequently show marked reduction in lumina. The renal pelvis is lined by normal appearing transitional epithelium. The submucosal tissues are heavily infiltrated with plasma cells and lymphocytes, in places mingled with acute inflammatory cells. The pelvic lumen, in some of the recesses, contains masses of polymorphonuclear leukocytes and a few blue-staining aggregates of calcific material.

"Sections from the cystic tumor shows varying sized cysts, some empty, some partly filled with pale-staining, amorphous material. The cysts are lined by a single layer of small, uniform-sized, cuboidal to flattened epithelium, having small, dark-staining nuclei showing no mitoses or atypism; this epithelial lining is absent in some portions of the various cysts. The walls of these cysts and the intervening tissue consist of relatively cellular, collagenous fibrous tissue containing focal and scattered lymphocytes and plasma cells. In addition, *small epithelial-lined acinar structures are seen throughout this stroma*; their lining cells are small, uniform in size, cuboidal, and have small, dark-staining nuclei; some of these acini are partly filled with eosin-staining amorphous material. *No glomerular structures are identifiable.* The renal pelvis in this portion is lined by transitional epithelium and the submucosal tissues are moderately infiltrated by lymphocytes and plasma cells. Irregular outpouchings of the renal pelvis into the polycystic mass are observed. However, *no direct communication between the cysts and the pelvis* is seen in the slides examined.

"Note: This kidney shows marked pyelonephritis. In addition, the upper half shows replacement of parenchyma by numerous varying-sized cysts. A feature is the downgrowth and filling of the renal pelvis by a 'stag-horn' shaped cystic mass, with its most pendant portion lodging snugly in the ureteropelvic junction. This pedunculated mass has the same histologic features of the tissues in the upper half of the kidney and apparently represents a downgrowth of this cystic tumor. The development of the hydronephrotic changes in the renal pelvis and calyces is no doubt related to the obstruction from this pedunculated tumor lying in the lumen at the ureteropelvic junction. The finding of small glandular acini in the fibrous intercystic stroma in the upper half of the kidney relates this lesion to an adenoma.

"In contradistinction to the usual type of polycystic disease, our case presents involvement of a portion of the parenchyma only. The lesion is considered to be benign and to have arisen on the basis of a congenital maldevelopment, a hamartoma.

"Diagnosis: 1) Adenoma, polycystic, benign, right kidney (upper half) with pedunculation into renal pelvis; 2) pyelonephritis, chronic, right kidney; 3) hydronephrosis, moderate, right kidney."

DISCUSSION

True *polycystic disease* of the kidney is almost always bilateral, and ultimately fatal. *Multilocular cysts* and *multicystic disease* of the kidney are separate and distinct entities lacking the serious import of polycystic disease since they involve only one kidney and are devoid of hereditary stigma.

Multicystic disease, as defined by Spence, consists of replacement of normal kidney by a conglomeration of varying sized cysts with no discernible renal parenchyma often associated with absence or atresia of the ureter. The pelvis may likewise be atretic or absent. The blood supply is variable and vascular pedicle may be lacking. This lesion is rare and almost always encountered in infants.

This is in marked contrast to the multilocular cyst, which, though equally rare, is found generally in elderly or middle-aged persons. Its cystic structure resembles that of polycystic disease, but is a sharply circumscribed lesion which does not involve the entire kidney, and glomeruli are not found in the stroma.

The case herein reported is unique in that the cystic mass did not exist solely as a parenchymal tumor, but herniated into the kidney pelvis as a large, globular, pedunculated tumor tightly distending the pelvis and causing it to enlarge in all dimensions. This mass assumed the normal contours of the pelvis and its distal extremity tightly plugged the ureteropelvic junction.

Of particular interest is the finding, on histological study of the stroma between the cysts, of aggregations of small epithelial-lined acinar structures suggestive of metanephric blastema (fig. 4). These cellular elements, though exceedingly sparse, characterize this tumor as a neo-

FIG. 4. Low (*A*) and high (*B*) power photomicrographs of cystic area. Acinar structures in connective tissue between cysts suggests metanephric blastema, as noted by Boggs and Kimmelstiel.

plasm and segregate it from the hamartomas, which are examples of dysplasia rather than neoplasia, as emphasized by Rusche (1952). This distinction has been stressed by Boggs and Kimmelstiel (1956) in an excellent paper in which they report a case with similar cytological elements. Probably all multilocular cysts would reveal similar findings on careful examination. Boggs and Kimmelstiel postulate that all multilocular cysts be regarded as tumorous in nature rather than a result of tubular dilatation due to congenital obstruction of portions of nephrons. Since these cellular elements resemble metanephric blastema, the proper terminology based on pathogenesis should be benign multilocular cystic nephroma.

RÉSUMÉ

An unusual case of multilocular cyst of the kidney is reported. The finding of embryonic structures in the stroma suggests a neoplastic pathogenesis rather than the dysplastic origin attributed to polycystic disease. Multilocular cysts cannot qualify as hamartomas since the latter by definition consist of a disorganized excessive focal overgrowth of *mature* normal cells.

450 Sutter St., San Francisco 8, Cal.

REFERENCES

ABSESHOUSE, B. S.: Serous cysts of the kidney and their differentiation from other cystic diseases of the kidney. Urol. & Cutan. Rev., **54:** 582–602, 1950.

BOGGS, L. K. AND KIMMELSTIEL, P.: Benign multilocular cystic nephroma. Report of 2 cases of so-called multilocular cyst of kidney. J. Urol., **76:** 530–541, 1956.

IVKER, M. AND KEESAL, S.: Multilocular cysts of kidney. AMA Arch. Surg., **81:** 798–802, 1960.

RUSCHE, C.: Renal hamartoma (angiomyolipoma): Report of 3 cases. J. Urol., **67:** 823–831, 1952.

SPENCE, H. M.: Congenital unilateral multicystic kidney: An entity to be distinguished from polycystic kidney disease and other cystic disorders. J. Urol., **74:** 693–706, 1955.

SPENCE, H. M., BAIRD, S. S., AND WARE, E. W. JR.: Cystic disorders of the kidney: Classification, diagnosis, treatment. J.A.M.A., **163:** 1466–1412, 1957.

DISCUSSION

DR. JOHN K. LATTIMER (New York, N. Y.): I should like to speak just for a moment about the matter of the multilocular cysts. In an analysis of some 650 children with masses in the abdomen, we found a half dozen of these.

(Slide) This was a child with an enormous mass in the left flank; but pushed way down at the bottom of the screen, over by the promontory of the sacrum, there are a couple of functioning calyces. The right kidney is normal.

(Slide) The next slide shows the mass in the flank with a capsule over it and a bit of kidney at the bottom. This mass is so huge that in making the incision into the abdomen, the abdominal wall snapped back. I was worried that I wouldn't be able to get it closed in case I couldn't get the tumor out. We sectioned it.

Incidently, before we sectioned it at the operating table, we put a needle into it to try to aspirate to see if it was one large mass. We could get only tiny amounts of clear fluid.

We took it out. (Slide) On section it showed this typical multiloculated cystic configuration about which Dr. Gibson has spoken.

(Slide) Some weeks later we had a similar case, a child with a large mass in the abdomen. We exposed the mass and found again a capsule, a bit of kidney at the bottom, a similar pyelogram.

(Slide) On section, it again showed this multicystic structure. We took it out the same way and were very much surprised when the sections were reported Wilms tumor.

Our point here is that when you do find this even on cut section, don't dismiss the possibility that it might be Wilms tumor simulating this very distinct entity that Dr. Gibson has spoken about and shown us so well.

DR. SAULS: The interesting thing that I would like to bring out for a moment in closing is that in two of these cases we have presented, the pathologic findings were entirely unsuspected prior to operation. They were problems of hydronephrosis of unknown etiology, both of them following an open operation on the renal pelvis of the upper ureter.

This is something that one should keep in mind if one encounters this in any patient who has undergone pyelolithotomy, ureterolithotomy, or pyeloplasty with no complications in the immediate postoperative period, but presenting itself months or perhaps years later.

PROGRESS IN URODYNAMICS*

DAVID M. DAVIS WITH THE COLLABORATION OF PAUL ZIMSKIND

For nearly three quarters of a century curious investigators have sought to learn the exact details of the mechanism by which urine is propelled from kidney to bladder. Unfortunately the methods available during most of this time were crude and unsatisfactory, and for the most part were such that studies had to be confined to experimental animals. For this reason progress was slow, and, as far as human beings were concerned, we could not even discover what the normals were. Without a knowledge of norms, it is impossible to learn very much about pathological states.

From experiments on dogs, it had been learned that the dog ureter, faced with resistance, could develop a very high expulsive force, up to 50 mm. Hg., in its lower portion, and much less than this in its upper portion. It is clear that this protects the kidney parenchyma by keeping the pressure in the pelvis low. In spite of excellent work by the comparatively few investigators who attacked this problem, a great many people were led astray by the fact that the ureter looks like a simple rubber tube, and assumed that contractions of the pelvis forced the urine through the ureter, much as the heart forces the blood through the arteries, or the bladder forces the urine through the urethra. This error is demonstrated by the complete failure of the numerous efforts that have been made to substitute for the ureter such inanimate objects as rubber, plastic and even metal tubes, and non-muscular tissues such as veins and tubes of fascia.

I attempted to collect the literature on this subject in a paper published in ANNALS OF SURGERY in 1954, entitled The Hydrodynamics of the Upper Urinary Tract, and in this paper suggested that the mechanics of the urinary tract be called Urodynamics, much as the mechanics of the circulatory system are called Hemodynamics.

In 1951 Willard Drake, Jr., at my suggestion, devised an apparatus for measuring the rate of flow of the voiding stream through the urethra. This, in conjunction with cystometry made possible an intelligent analysis of the mechanics of the lower tract, and provided a reliable means of determining whether an inadequate flow through the urethra was due to obstruction or to diminution of the expulsive force of the bladder.

In 1957 Fredrik Kiil published in this country his magnificent study of The Function of the Renal Pelvis and Ureter. He demonstrated that the presence of very small catheters in those organs did not interfere with their normal activity in any way except in locations where the catheter had to pass through an already small stricture. However, when this occurred, a very typical form of pressure curve was produced, which was in itself diagnostic (fig. 6). Pressure changes were measured with transducer, amplifier and recording oscillometer. In the very restricted spaces existing in the upper urinary tract, any other form of manometry is completely unreliable owing to the relatively large fluid movement necessary to record pressure changes.

As soon as the Kiil method was published, I became convinced that it must very soon take its place as a routine diagnostic method in urology, but that its full usefulness would have to be preceded by a very large experience with normal and diseased urinary tracts in order that we might learn what the norms are, and the manner and degree in which departures from these norms occurred in diseased conditions. Urologists generally were slow to take up this new method.

I was finally able to obtain adequate funds, and after studying the various types of apparatus obtainable, I settled upon a so-called minipolygraph made by the Gilson Medical Electronics, of Middleton, Wisconsin. This apparatus has the advantages of being small, light, easily portable, easily adjusted, and rugged—all of which qualities fit it for clinical use. In our department, thanks to the enthusiastic co-operation of its head, Dr. Theodore R. Fetter, the apparatus is kept in the urology out-patient department, where roentgenographic facilities are available. All can be prepared for examination and the instrument calibrated in 20 or 30 minutes.

Our program is for a protracted series of

* These studies were supported by the Buck Urodynamics Fund, Jefferson Medical College, Philadelphia, Pa.

observations of all types of cases, and of as many normal individuals as possible, over a period of at least a year, at which time we hope to be able to present a really instructive study. Meanwhile, I would like at this time to present a few cases which may suggest how revolutionary the precise knowledge of urodynamics will probably be.

FIG. 1. Case 1. Intravenous urogram diagnosed a s normal.

CASE REPORTS

Case 1. A. S., No. 133462, a 20-year-old Negress, was first seen becaue of an episode of acute cystitis and left pyelonephritis. She had had no prior urologic symptomas.

After appropriate antibacterial chemotherapy, cystoscopy was performed, disclosing minimal elevation of the posterior lip of the bladder neck. Both ureteral orifices were stenotic, especially on the left, where a size 4F ureteral catheter met obstruction at the meatus.

The intravenous urogram (fig. 1) shows pelves which can be called normal and in fact nothing out of the way except perhaps a slightly excessive filling of the lower left ureter.

The pressure curve (fig. 2) shows only for the left ureter. In the upper ureter, the contraction pressures reach a figure of over 50 mm. Hg. In the lower ureter, to the right of the illustration, the contraction pressures fall to about 40 mm. Hg., still very high, and the resting pressure to about 25 mm. Hg. All this with no clearly demonstrable ureterectasis! Obviously, the ureter does not dilate until it has given up the fight against obstruction. Only then does it dilate, like the cardiac ventricle or the bladder, and the pressures then are, as Kiil has shown, surprisingly low.

Case 2. G. B., No. 133755, a 30-year-old white woman, noted the onset of frequency, pyuria, dysuria, nocturia and hematuria in 1957. An ulcer of the bladder was diagnosed and fulgurated. Her symptoms recurred promptly, and in 1959 a

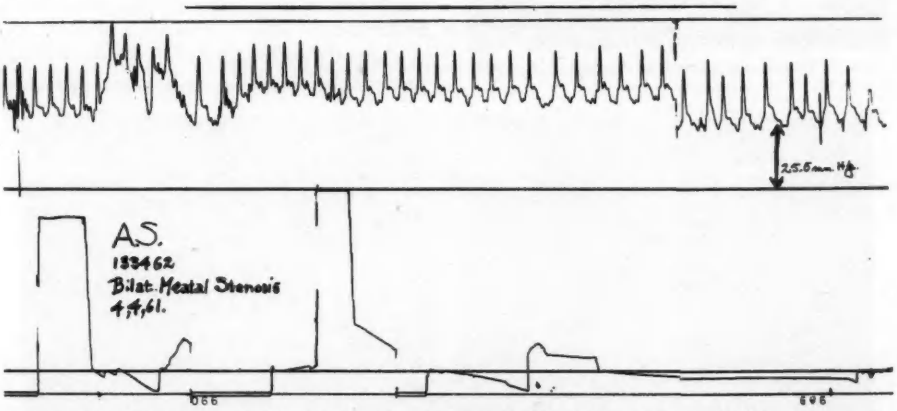


FIG. 2. Case 1. Pressure graph of left ureter. Left portion is at 25 cm. above bladder. Contraction pressures of 50–55 mm. Hg., resting pressure very high, around 35 mm. Hg. Right portion is at 10 cm. above bladder with contraction pressures around 40 mm. Hg. and resting pressure 25.5 mm. Hg.

suprapubic cystostomy was established and maintained for 6 months. In September 1960, a transurethral resection of the vesical orifice was done, followed by improvement for several months, after which her symptoms returned.

At the time of cystoscopy in April 1961, the urethra was quite snug to a 28F panendoscope. The mucosa exhibited scattered areas of edema, with cystic and erythematous change at the posterior wall. No ulceration or trabeculation was seen. The ureteral orifices were stenotic bilaterally. The vesical orifice was irregular and mildly contracted.

FIG. 3. Case 2. Intravenous urogram. Diagnosed as normal.

Here, in spite of cystoscopically demonstrated obstruction at both ureteral meatuses and vesical orifice, the intravenous urogram could be, and indeed was, called normal (fig. 3).

The pressure graphs (fig. 4), taken at a level 23 cm. above the bladder, show resting pressures of about 9 or 10 cm. of water (7.3 mm. Hg.) on both sides, with contraction pressures definitely higher on the right, i.e. maxima of 37 cm. H_2O, (27.3 mm. Hg.), on the left, 56 cm. H_2O (41.6 mm. Hg.) on the right. This would indicate that while the right ureter shows some hypertensive reaction to obstruction, the principal trouble for this patient is a still inadequately treated vesical orifice obstruction.

Case 3. K. L., No. 105740, an 18-year-old Negress, was 7 months pregnant when she noted the onset of intermittent right flank pain radiating to the right groin, frequency, burning, and pyuria. Her symptoms responded to chemotherapeutic agents. She experienced a similar episode 2 months after delivery.

Two weeks later, after appropriate chemotherapy, cystoscopy was performed and revealed urethral stenosis with a normal bladder mucosa. The ureteral orifices were stenotic bilaterally. A size 5F catheter was passed with resistance at each meatus, especially marked on the right.

Figure 5, *A* shows what looks like a normal intravenous urogram. However, figure 5, *B*, taken later, shows that the left kidney and ureter are completely empty, while on the right side the ureter is completely full from top to bottom, but not greatly distended, while the right pelvis could scarcely be called hydronephrotic.

Figure 6 shows a slightly but definitely elevated pelvic pressure on the right, markedly elevated

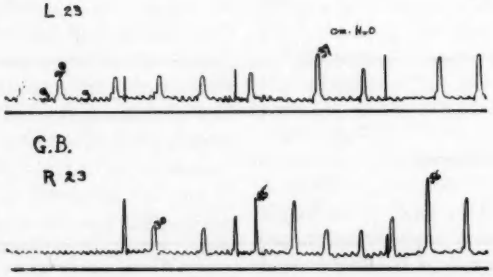


FIG. 4. Case 2. Pressure graphs, bilateral. L 23 is left ureter 23 cm. above bladder, R 23 is right ureter 23 cm. above bladder. Contraction and resting pressures are shown in cm. of H_2O.

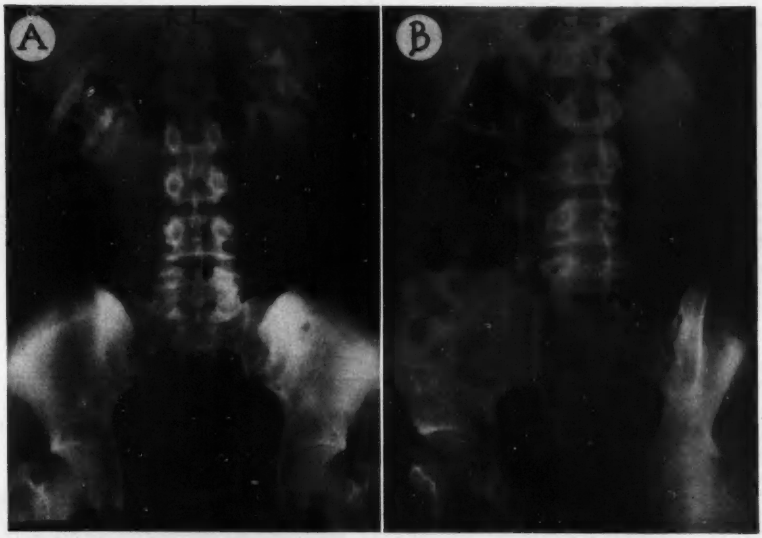


FIG. 5. Case 3. Intravenous urograms. *A*, 10 minute film. *B*, 30 minute film. Note right ureter filled from end to end.

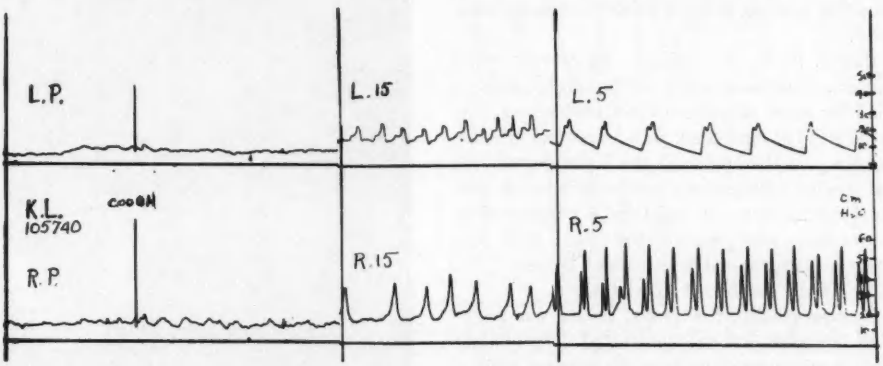


FIG. 6. Case 3. Pressure graphs, bilateral. L. P. and R. P., left and right pelvis; L 15 and R 15, left and right ureters 15 cm. above bladder; L 5 and R 5, left and right ureters 5 cm. above bladder. Note higher pelvic pressure on right, and resting pressure falling on L at 5 cm., rising on R at 5 cm. This indicates lower ureteral narrowing on right.

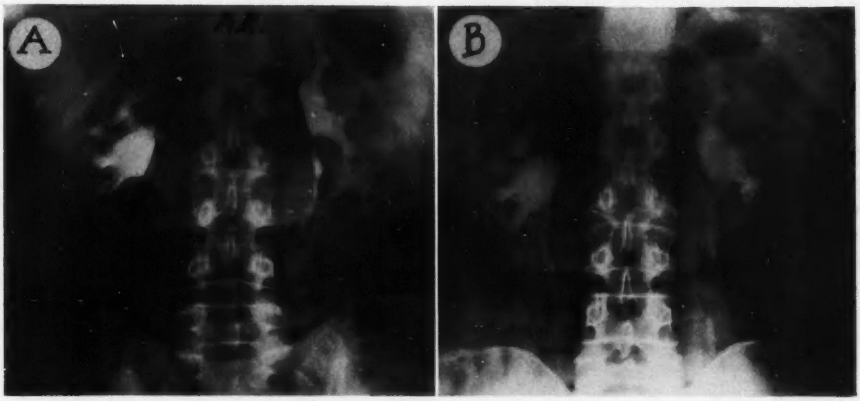


FIG. 7. Case 4. Intravenous urograms. *A*, 15 minute film. *B*, 30 minute film

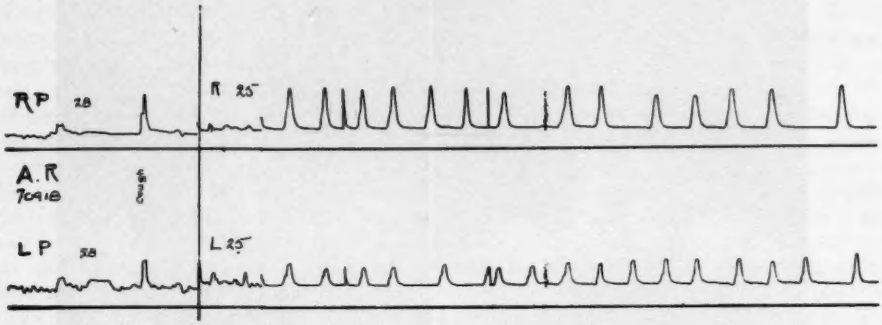


FIG. 8. Case 4. Pressure graphs, bilateral. R. P. and L. P., right and left pelves; R 25 and L 25, right and left ureters 25 cm. above bladder. Note higher contraction pressures in right ureter.

ureteral contraction pressures at 15 and 5 cm. on the right, and elevated resting pressure in the right lower ureter. Here is a definite lower ureteral obstruction, well compensated, and therefore nothing to show for it roentgenographically.

Case 4. A. R., No. 70918, a 54-year-old white woman, underwent right nephro-ureterolysis in 1955 for relief of ureteropelvic obstruction. She noted relief of right flank pain for several months, but the pain then recurred to a lesser degree. She was treated with periodic ureteral dilatation with short-lived benefit. In addition, a vesicourethral contracture was present, associated with frequency, nocturia and intermittent dysuria. This had partially responded to dilatations.

Cystoscopically, the vesical orifice was somewhat irregular, but not contracted. The bladder mucosa was normal, as were the ureteral orifices. A size 4 catheter met minimal resistance at 27 cm.

Figure 7, two films of an intravenous urogram, shows slight hydronephrosis on both sides in the later film, *B*. No one could tell from this film which side is more diseased, but the pressure graphs (fig. 8) show clearly how much harder the right ureter is working to expel the urine. In both pelves the pressure is somewhat high (8–9 mm. Hg.) and contraction waves (possibly they might be called "trigger" waves for ureteral peristaltic waves) are more conspicuous than normal.

Case 5. M.H., No. 73056, a 58-year-old white woman, was first seen in 1958 because of increasing frequency and nocturia several years in duration. Cystoscopy at that time revealed a

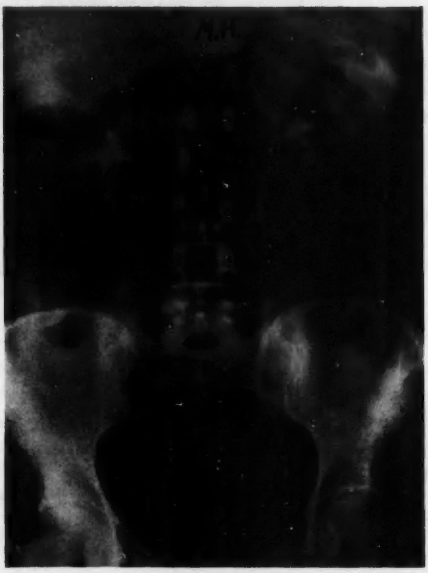


FIG. 9. Case 5. Intravenous urogram. Note left ureter filled from end to end.

narrow vesical outlet with no trabeculation evident in the bladder. She was treated with periodic urethral dilatation, and improved symptomatically for several months at a time. At no time were bacteria noted in the urine.

At cystoscopy, polypoid changes were noted at the vesical orifice, which was contracted. The ureteral orifices were not remarkable.

Figure 9, an intravenous urogram, shows remarkably normal looking pelves, with razor-sharp calyces. The left ureter, however, is full

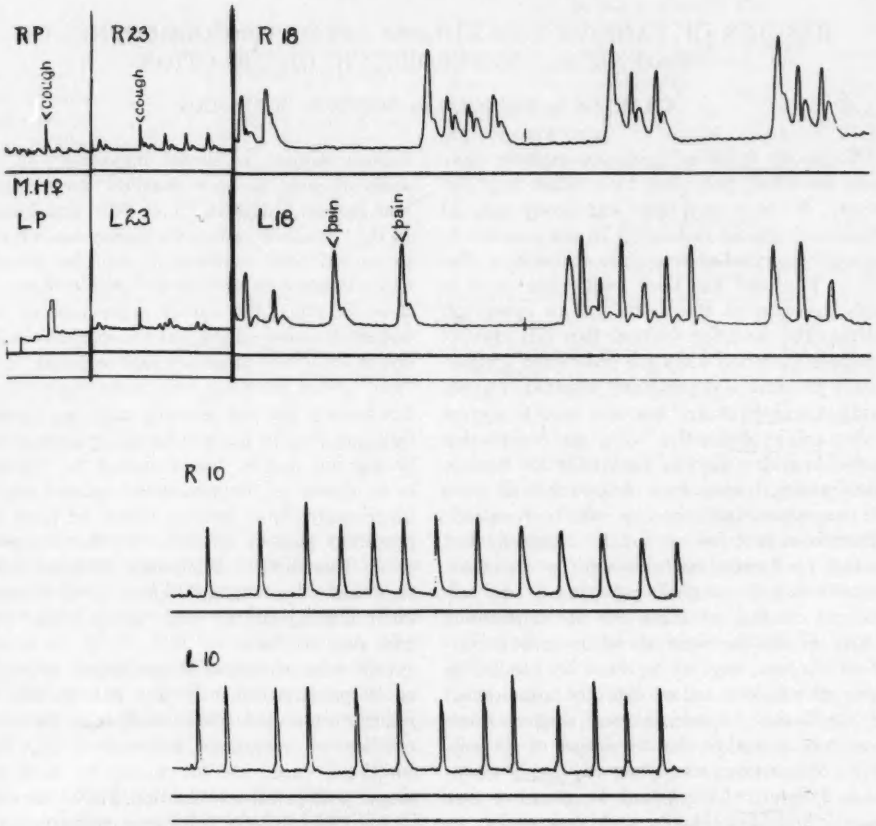


FIG. 10. Case 5. Pressure graphs, bilateral. R. P. and L.P., right and left pelves; R 23 and L 23, right and left ureters 23 cm. above bladder; R 18 and L 18, right and left ureters 18 cm. above bladder; R 10 and L 10, right and left ureters 10 cm. above bladder. Note grouped contraction waves at 18 cm. and left side pain at time of contraction wave.

from top to bottom, always a sign of abnormality, though little, if any, wider than normal.

The graphs are shown in figure 10. Pelvic pressures are the same on both sides (10 cm. H_2O, or 7.3 mm. Hg.). At 23 cm., the contraction waves are irregular on both sides. At 18 cm., the real story appears; contraction pressures to 60 cm. H_2O (44.2 mm. Hg.), elevated resting pressures, grouped contraction waves, tell of the strong efforts of the ureters to expel the urine. On the right side, the resting pressure climbs at 18 cm., but drops off at 10 cm., obviously an obstruction between 10 and 18 cm. On the left, less rise in resting pressure occurs, but pain with each contraction, an unusual finding. Does this suggest a progressing obstruction on the left to which the organs are less accustomed?

These few graphs prove little or nothing, but I trust that it is obvious how excitingly promising they are. One thing seems sure already; we now have a method which will disclose obstructions not demonstrated by intravenous urography—perhaps not by any other method! At very least, the concept of a non-obstructive pyelonephritis will have to be drastically revised. If this can be done, it will spell hope of relief for large numbers of patients who have been persuaded that their condition is hopeless.

Haverford Square Building, Haverford, Pa.

RESULTS OF VARIOUS PROCEDURES USED FOR CORRECTION OF CONGENITAL URETEROPELVIC OBSTRUCTION

CHARLES L. PRINCE AND PETER L. SCARDINO

Numerous types of pyeloureteroplasty have been described, but most have fallen into disrepute. We have used three well-known surgical procedures almost exclusively in our practice to correct congenital ureteropelvic obstruction. The Foley Y plasty[1] has been used when there is high insertion of the ureter on an extrarenal pelvis. The so-called vertical flap procedure[2, 3] has been preferred when the obstructed ureteropelvic juncture is dependently situated. Davis's intubated ureterotomy[4] has been used to correct ureteropelvic obstruction when the constriction is too long or otherwise unsuitable for revision with existing tissues. It is obvious that all cases of congenital obstruction at the ureteropelvic juncture cannot be so simply classified, and cannot be handled satisfactorily by the three aforementioned surgical procedures. An occasional unusual situation will be encountered which will tax the ingenuity of the most experienced surgeon, and which must be handled in some other fashion, not infrequently in an original or unorthodox manner. A good surgical result from any procedure for correction of ureteropelvic obstruction presupposes 1) relief of symptoms, 2) return of the kidney to normal or near normal both functionally and structurally, as demonstrated by pyelography; and 3) uninfected urine. To accomplish these results the surgical procedure must establish a transition between the renal pelvis and ureter with three prime features: 1) adequate caliber, 2) dependent position, and 3) funnel shape. Classification of results following ureteropelvic surgery is admittedly difficult, and is of necessity dependent upon personal judgment and individual variations. For this reason, comparison of results of various authors is almost impossible. In this series of cases we have classified our results in four groups: Excellent, Good, Fair, and Failure. In the "excellent" group the kidney has returned to normal both anatomically and functionally. Cases classed as having a "good" result are those in which the kidney approaches normal, but is not quite perfect, but the surgical result is one of which any surgeon would be proud. In the "fair" group there has been some improvement functionally and anatomically, and no persisting infection, but the kidneys remain hydronephrotic in varying degree. Cases classed as "failure" have shown no improvement anatomically or functionally, have become worse, or have had persistent pain or infection or other complications. Therefore, in this series, all cases except those classed as "failure" have shown improvement, although in the "fair" group it may have been very minimal.

Our series consists of 82 operations performed on 80 patients (table 1). Ten patients did not return for postoperative evaluation, so the actual number of operations followed is 72. Five additional cases are too recent to have had proper postoperative evaluation. Failure occurred in 9 or 12.5 per cent. This figure compares favorably with the results obtained by Creevy,[5] who reported 15 per cent failures in 73 Y plasties. However, our failure record is almost double that of Culp,[6] who recently reported failures in 6.3 per cent of his cases following all types of pyeloureteroplasty. This series of 223 cases is the largest of which we are aware. Culp, however, classified his cases as either "success" or "failure," and all of the 14 cases in his failure group required secondary surgery (either nephrectomy, nephrostomy or secondary plastic procedures). By the same criteria only 6.9 per cent of our cases would have been classed as failures, a figure

[1] Foley, F. E. B.: A new plastic operation for stricture at the ureteropelvic juncture; report of twenty operations. J. Urol., **38:** 643, 1937.

[2] Culp, O. S.: A pelvic flap operation for certain types of ureteropelvic obstruction; preliminary report. Proc. Staff Meet., Mayo Clinic, **26:** 483, 1951.

[3] Scardino, P. L. and Prince, C. L.: Vertical flap ureteropelvioplasty: Preliminary report. South. Med. J., **46:** 325, 1953.

[4] Davis, D. M.: Intubated ureterotomy: A new operation for ureteral and ureteropelvic stricture. Surg., Gynec. & Obst., **76:** 513, 1943.

[5] Creevy, C. D. and Helenbolt, K. S.: The results of "Y" plasty after five to twenty-four years: A review of seventy-three operations. J. Urol., **77:** 388, 1957.

[6] Culp, O. S.: Choice of operations for ureteropelvic obstruction: Review of 385 cases. Read at meeting of Canadian Urological Association, Banff, Alberta, Canada, July 1 to 3, 1960.

TABLE 1. *Results*

Total cases	82 (80 patients)
Not followed	10
Followed	72 (4 mos.–14 yrs.)
Poor (failure)	9 (12.5%)
Fair	18 (25%)
Good	22 (30.5%)
Excellent	23 (31.9%)

TABLE 2. *Results: Good or excellent*

	No. Followed	Results—Good or Excellent	Per cent
Vertical flap	34	21	61.7
Int. ureterotomy	28	19	67.9
Y-V plasty	7	2	28.5
Other	3	3	100

TABLE 3. *Results: Fair*

	No. Followed	Results Fair	Per cent
Vertical flap	34	9	26.5
Int. ureterotomy	28	6	21.4
Y-V plasty	7	3	43.0

TABLE 4. *Failures*

	No. Followed	Failures	Per cent
Vertical flap	34	4	11.7
Int. ureterotomy	28	3	10.7
Y-V plasty	7	2	28.6
Other	3	0	0

remarkably close to that of Culp. In retrospect, our failure percentage would have been somewhat lower had our zeal and enthusiasm during the early days of the vertical flap procedure not caused us to do this operation several times when the kidney was obviously beyond salvage. Another case, also included in the failure group, was initially a poor result, but is now greatly improved following a secondary vertical flap plasty.

In an effort to determine the efficacy of the three procedures we have tabulated the "good" and "excellent" results obtained with each procedure (table 2). Perfect or near perfect results were obtained in 45 of the 72 cases (62.5 per cent). In our series surgery resulted in normal pyelograms and absence of pain or infection in 32 per cent of the cases. Culp reported the same results in 42 per cent of his cases, but the interpretation of a pyelogram as "normal" depends upon many factors, most important of which is the personal opinion of the interpreter, which obviously must vary. Thus, comparison of this type is most difficult. Fair results were obtained in 18 or 25 per cent (table 3). The failures are broken down in table 4. The results obtained from the vertical flap procedure and from intubated ureterotomy have been almost identical in all groups. The poor results and higher percentage of failure obtained with the Y-plasty may be attributed in part to the fact that each of the seven procedures was performed on a kidney showing grade 4 hydronephrosis. However, with extreme degrees of hydronephrosis (table 5), both vertical flap procedures and intubated ureterotomies seem to fare considerably better than Y-plasties, and again the difference between the results obtained with the first two procedures was minimal.

Calculi were present in the affected kidney in 15 of the 82 cases or 18.3 per cent (table 6). They were multiple in 8 cases and a single calculus was present in seven. It is of interest that there were 7 patients in this series over 50 years of age who underwent ureteropelvioplasty, and every one of these patients over 50 had one or more stones in the affected kidney. The oldest patient was aged 80, and he had 4 calculi in the hydronephrotic kidney, and a staghorn calculus in the opposite side. He obtained a good result. We do not feel that the presence of stones preoperatively has any effect on the surgical outcome.

Thirty-nine per cent (28) of the obstructed kidneys were infected preoperatively. To determine whether or not infection influences the surgical outcome, the results in these cases are compared with the over-all results in table 7. It is apparent from these figures that preoperative infection does not affect the end result.

Except in the case of Davis's intubated ureterotomy, where splinting is prerequisite, there is no general agreement as to its value. The splinters and the non-splinters seem to be about equally divided, with some always using a splinting catheter, and others never using one. We prefer not to use a splint, but do not hesitate to do so

TABLE 5. *Results with extreme degrees of hydronephrosis*

	No. Followed	Excellent	Good	Fair	Poor
Vertical flap	24	8 (33.3%)	8 (33.3%)	5 (20.8%)	3 (12.5%)
Int. ureterotomy	18	5 (27.7%)	6 (33.3%)	5 (27.7%)	2 (11.1%)
Y-V plasty	7	2 (28.6%)	—	3 (42.6%)	2 (28.6%)

TABLE 6. *Results with associated calculi*

No. Cases	Excellent	Good	Fair	Poor	Lost
15 (7 single) (8 multiple)	5	2	7	0	1

TABLE 7. *Results with associated infection (28 cases) compared with over-all results*

	Infected Cases %	Over-all Results %
Excellent	28.6	31.9
Good	28.6	30.5
Fair	35.7	25.0
Poor	7.2	12.5

TABLE 8. *Results with use of splints*

	Excellent	Good	Fair	Poor
Vertical flap	3	5	2	1
Y-V plasty	1	0	2	2

TABLE 9. *Symptomatic relief when functional and anatomic results were only fair or poor (27 cases)*

100%	14
75%	5
50%	3
0%	5

TABLE 10. *Secondary procedures*

Cystoscopic stone extraction	2
Ureterolithotomy	1
Pyelolithotomy	1
Nephrectomy	4
Vertical flap plasty	1

(Stones developed postoperatively in 5 or approximately 7% of cases)

when we feel one is indicated or might be helpful. In this series a splint was used only 16 times (table 8), and with no discernible effect on the outcome.

An interesting and striking feature that we have noted is the frequency with which the patient is completely or almost completely relieved of all symptoms, even though the functional and anatomic result obtained has been only "fair," or a "failure" (table 9). Over half of the patients in this group were completely relieved of their symptoms and infection, in spite of an apparently poor surgical result. Only five of the 27 cases in these groups obtained no symptomatic relief whatever.

Table 10 shows the chief complications encountered and the procedures required for correction. Aside from failure of the plastic procedure, the most common complication was stone formation, which occurred in five or approximately 7 per cent of the cases. One patient passed the stone spontaneously, but secondary open surgery was required in 2 instances, and a ureteral calculus was removed cystoscopically in 2 cases. It should be noted that in four of the 5 cases in which stones developed postoperatively, a splint of some type was used from 3 to 5 weeks. In the fifth case, no splint was used, but stones were present in the kidney preoperatively. This would strongly suggest that the use of a splint increases greatly the possibility of postoperative stone formation. The secondary vertical flap plasty has already been mentioned. Even though the surgical result itself has been classed as a failure in 9 instances, only four (5.5 per cent) of these patients have required subsequent nephrectomy. Two nephrectomies have been done following vertical flap plasties, and one each after Y plasty and intubated ureterotomy. Of the remaining four, one will probably require nephrectomy in the future, but the other three are doing surprisingly well symptomatically, in spite of a poor functional and anatomical result.

SUMMARY AND CONCLUSIONS

A series of 72 ureteropelvioplasties of various types performed for correction of congenital ureteropelvic obstruction has been presented.

In our practice, the vertical flap plasty, the intubated ureterotomy of Davis, and the Foley Y plasty have been used almost exclusively for the correction of this condition.

In our hands, the results obtained from the vertical flap procedure and intubated ureterotomy have been quite superior to those obtained from the Y plasty. The results obtained with the first two mentioned procedures have been almost identical.

In this series, perfect or near perfect results were obtained in 62.5 per cent of the cases, and "normal" pyelograms resulted in 32 per cent.

By our criteria, failure of the operative procedure resulted in 12.5 per cent of the cases, but nephrectomy following apparent surgical failure has been necessary in only 5.5 per cent.

The presence of calculi or infection in the kidney prior to operation apparently has no effect on the outcome of the plastic procedure.

Postoperative stone formation occurred in 7 per cent of the cases, and our experience indicates that postoperative splinting increases greatly the possibility of stone formation.

2515 Habersham St., Savannah, Ga.

DISCUSSION

Dr. T. Leon Howard (Denver, Col.): I should like to make a few remarks on this plastic operation on the kidneys. We thought this thing out many, many years ago, and always with the same conclusion, that the patient's symptoms were relieved although the results were disappointing as far as the pyelograms showed. In my opinion, when you handle a kidney and do a surgical procedure on the pelvis of that kidney, you practically do a sympathectomy on that kidney. Consequently, the symptoms disappear because the pain disappears because the sympathetic nerves have been destroyed to a great extent. Consequently, that patient is relieved of the pain although we are disappointed in the after results.

Many years ago, Roy Henline read a paper in which he reported a great many of these cases with bad results, but the patient was relieved of pain. We don't take into consideration trauma and probable destruction of the sympathetic nerves that supply the pelvis of that kidney and start out peristaltic waves. We have to take that into consideration when these patients are perfectly happy with the result and you are perfectly happy because the patient's symptoms disappear.

Dr. Davis: I would like to say, in connection with Dr. Howard's discussion, that with increasing knowledge that we now have of the normal intrapelvic pressure, a necessary sequel of operations to relieve obstructions in the ureteropelvic junction or lower down in the ureter may very well be the obtaining of intrapelvic pressure through a nephrostomy tube before removing the nephrostomy tube. Thus, with the x-ray observations, the fact that the pelvis is emptied within a 10-minute period and if the intrapelvic pressure is normal, we may then remove the nephrostomy tube with complete confidence that the fistula will close immediately and that we will have a good result.

This is a little bit against the feeling of those who think that the nephrostomy tube is a bad thing. To me, it seems like a device to keep us in control of a situation so that we know confidently when we remove the nephrostomy tube that the result is going to be a good one. This we can be sure of if the pelvis empties within ten minutes and the pressure within it is normal.

BLADDER CALCULI FORMED AROUND RETAINED FRAGMENTS OF RUPTURED FOLEY CATHETER BALLOONS

RICHARD CHUTE

From the Veterans Administration Hospital, Boston, Mass.

Now and then the balloon of a Foley catheter bursts, and when this happens, rarely a piece of the balloon—perhaps the size of a fingernail—is blown off as a free fragment and remains in the bladder. If this sank to the bottom of the bladder, it would probably soon be passed when the patient voided. Unfortunately, however, this fragment floats on the urine up at the top of the bladder and thus may elude expulsion. Soon—as is the case with any foreign body in the urinary tract—a deposition of urinary phosphates takes place on this fragment and it sinks to the bottom of the bladder. By this time it has usually become too unwieldy and stiff with its coating of phosphates to be voided out, and remains in the bladder as a nidus upon which urinary phosphates continue to be deposited to form a calculus eventually.

In our Veterans Hospital, we have a number of long-term chronic incurable neurological patients who are on constant bladder drainage by catheter—often tidal drainage—in whom bladder calculi form occasionally, and, rarely, around a fragment of a ruptured Foley catheter balloon. Since the formation of bladder calculi in such patients is not rare, they are checked at intervals, and any calculi which form are removed transurethrally.

However, there is another category of patients, in whom the formation of a bladder calculus around a fragment of a ruptured Foley catheter balloon is an unwelcome and very undesirable surprise. These are patients in whom such a calculus develops as a late sequel to a period of constant bladder drainage, usually in connection with a prostate operation. During the past 2 years, we have had occasion to operate upon eight such patients. If the calculus gave rise to signs or symptoms leading to its detection before it had grown too large, it was crushed and removed (2 cases); but if it was not discovered until it was too large to crush (which was more often the case) suprapubic cystolithotomy was necessary (6 cases). We have found that whenever a calculus has occurred as a late sequel to a prostate operation or to a period of catheter drainage—whether or not there is a history of a ruptured Foley catheter balloon—the calculus almost invariably contains a piece of rubber balloon as a nidus in the center, about which the stone has formed. Such calculus formation is a late sequel, as the shortest time in which one has been detected was 10 months, while the longest time was nearly 3 years.

The formation of such a calculus, especially if it necessitates surgical cystolithotomy, is most unfortunate for several reasons. First, and most important, the patient, who often is elderly and quite possibly a poor operative risk, is now compelled to undergo another operation with its attendant risks and discomforts, not to mention the expense involved to him or to his family and/or his insurance company, if he is a private patient—or, if he is not a private patient, to the city, state, or Veterans Administration, etc. Also, if he is working, he will lose considerable time from his job. Should the patient refuse surgery, he is condemned to endure his symptoms, which will probably get worse as the stone gets larger, and will almost surely eventually drive him to surgery willy-nilly. Secondly, the formation of many such calculi can be prevented, as will be discussed later. Thirdly, this untoward happening contains the potential for much grief for the attending physician. Nowadays, any private patient who discovered that such a calculus had been due to a fragment of Foley catheter balloon retained after surgery would be very apt to sue the attending surgeon, claiming negligence or "assault" or some error for which the physician in charge was suable, which had caused him to be subjected to the pain and risk of another operation, to considerable hospital and professional expenses, and to loss of time from his job. A legal opinion on this matter was obtained from a member of a well-known law firm in Boston. His opinion was that, while he had never heard of a suit arising from this particular happening, he felt that the physician in charge would probably be sued, and that he and/or his insurance

company would probably be found liable and would have to pay heavy damages. In addition, the publicity which might possibly be associated with such a suit might well be damaging to the professional reputation of the physician involved.

In order to guard against the untoward occurrence of such secondary calculus formation around a fragment of a Foley catheter balloon, on our service whenever a Foley catheter comes out of a patient due to balloon rupture, it is absolutely mandatory for whomever discovers this to be very sure to save the catheter to be shown to one of our doctors. If, on careful examination of the catheter, there is any doubt or suspicion whatsoever that a piece of the balloon is missing, it is mandatory to cystocope the patient before he leaves the hospital. While we have done some cystoscopies which have proved to be unnecessary, we have also on several occasions discovered a fragment of balloon floating up by the air bubble, and removed it cystoscopically, thereby preventing future trouble. This is an important matter, and sad experience has taught us not to take the rupture of a Foley balloon too lightly. Since the piece of balloon floats on the urine or irrigating fluid up near the air bubble, it is important to use the usual cystoscope with right-angle vision, since the panendoscope does not visualize this area easily. Thus in one of our cases, the fragment known to be missing from the balloon was not detected by the panendoscope, although it was later proven to have been present in the bladder, doubtless up near the air bubble where it was not seen.

Urologists are not the only physicians who use Foley catheters. General surgeons, gynecologists, obstetricians, orthopedists, neurologists, neurosurgeons, and even on occasion internists use Foley catheters, and they should be aware of these possibilities.

A representative of the largest manufacturer of Foley catheters in this country was contacted relative to making the rubber of the balloon roentgen-opaque, so that a fragment retained in the bladder could be detected by x-ray. After consultation with headquarters, the opinion was given that the addition of material to the rubber to render the balloon roentgen-opaque would affect its strength and distensibility so unfavorably that it was not advisable. Perhaps some way of accomplishing this will be found eventually.

FIG. 1. Case 1. *A*, plain x-ray (KUB) shows large calculus in bladder. *B*, bladder calculus, split in half, shows fragment of rubber Foley catheter bag in center. Size indicated by comparison with fifty-cent piece.

ILLUSTRATIVE CASE REPORTS

Case 1. J.B. underwent bilateral orchiectomy and transurethral resection for proven carcinoma of the prostate in January 1958, at the age of 64. There was no mention on his record of a Foley catheter balloon having ruptured. He was discharged on a maintenance dose of 1 mg. stilbesterol daily and did very well until he was readmitted to the hospital in December 1960, 35 months later, with a several months' history of increasing frequency, dysuria and a small stream. His prostate was small and soft and not obstructing, but he had a golf ball-sized round stone in his bladder. This was removed by suprapubic cystolithotomy. Convalescence was satisfactory and the patient is now free of bladder symptoms. On cracking the stone a piece of rubber Foley catheter balloon, the size of a fingernail, was found in the center of the stone (fig. 1).

Case 2. L.P., aged 65, underwent combined transvesical-retropubic prostatectomy for benign prostatic hyperplasia in December 1958. There is a note in his record that on the fifth postopera-

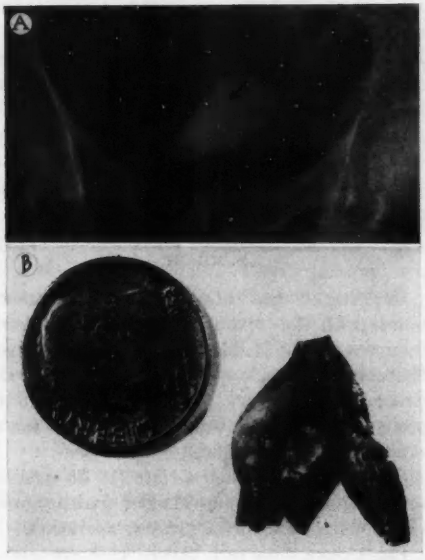


FIG. 2. Case 2. *A*, plain x-ray (KUB) shows large bladder calculus with area of decreased density in its center. *B*, photograph shows fragment of rubber consisting of major portion of Foley catheter bag, found in center of bladder calculus. Size indicated by comparison with dime.

FIG. 3. Case 3. *A*, plain x-ray (KUB) shows large bladder calculus. *B*, bladder calculus has been broken into fragments. Photograph shows piece of rubber Foley catheter bag (see arrows) in center of calculus. Size indicated by comparison with dime.

tive day his Foley catheter came out because of rupture of the balloon, and another catheter was inserted, but he was not cystoscoped. In October 1959, 10 months later, he re-entered the hospital complaining of difficulty in voiding and burning urination for about 6 weeks. A plain x-ray (KUB) showed a thumb-sized bladder calculus with a central curvilinear area of decreased density. Litholapaxy was first tried but the stone was too big, and it had to be removed by suprapubic cystolithotomy. The patient made a satisfactory recovery and his symptoms were relieved. A large fragment of rubber, consisting of the major portion of a Foley catheter balloon, was found in the center of the stone (fig. 2).

Case 3. E. S., a man of 65, had a transurethral prostatic resection for benign hyperplasia in August 1959. During the third postoperative night the Foley catheter came out due to rupture of the bag, and examination of this indicated that part of it was missing. Consequently, before the patient went home, his bladder was examined by a resident using a panendoscope only, but no piece of bag was found. (If the usual cystoscope with right angle vision had been used, probably a piece of rubber floating up near the air bubble would have been detected.) In October 1960, 14 months later, the patient re-entered the hospital quite sick with pneumonia. When he was convalescent, intravenous urography was done because of pyuria, and a thumb-sized bladder calculus was revealed. The patient was sent home for 4 months to regain his strength, and then returned in February 1961, when the stone was removed by suprapubic cystolithotomy. He withstood the procedure satisfactorily and by now feels pretty well. On cracking the calculus a piece of rubber Foley catheter balloon, the size of a fingernail, was found at its center (fig. 3).

Case 4. J. M. had a 15 year history of chronic duodenal ulcer with bleeding episodes for which he had a partial gastrectomy in September 1959 at the age of 46. Postoperatively he had pneumonia, and then a dehiscence of his wound, requiring resuturing. A subphrenic abscess de-

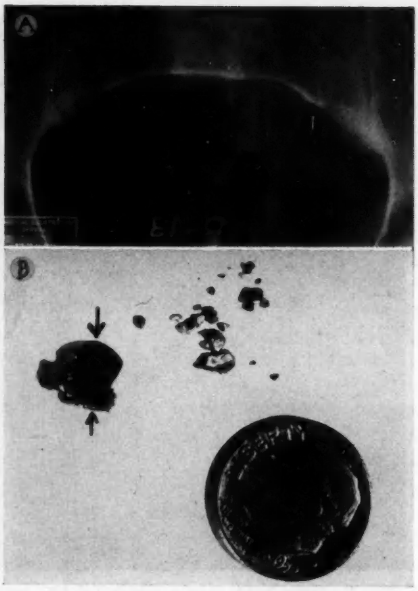


FIG. 4. Case 4. *A*, plain x-ray (KUB) shows bladder calculus size of small raspberry with area of decreased density in its center. *B*, fragment of rubber Foley catheter bag found in center of bladder calculus when it was crushed by litholapaxy and washed out. Also shown are a few pieces of calculus and dime to indicate comparative size.

veloped and had to be drained. He was so sick and weak at this time that he was maintained on Foley catheter constant drainage for some weeks. There is no note in his record of a Foley catheter balloon having ruptured, but this must have happened. In December 1960, a little more than a year later, he had some urinary symptoms and an x-ray showed a raspberry-sized bladder calculus in the center of which was an area of decreased density. The stone was crushed by transurethral litholapaxy, and in its center was found a little fingernail-sized fragment of a Foley catheter balloon (fig. 4). The stone fragments and the rubber were washed out transurethrally, and the patient's symptoms improved.

SUMMARY

Occasionally the balloon of a Foley catheter bursts with the separation of a piece as a free fragment in the bladder. Since such a fragment floats on the urine, it may not be expelled. In this circumstance, urinary phosphates are soon deposited on it, and it will act as a nidus for an eventual bladder calculus.

Such calculi are found as late (10–35 months) complicating sequelae to bladder drainage, usually in connection with a prostate operation.

Eight cases with such calculi, each containing a fragment of rubber balloon as a central nidus, have been operated upon in the last 2 years on the author's service. Four illustrative cases are reported.

The occurrence of this type of iatrogenic secondary calculus is most unfortunate for the patient as he is compelled to undergo another operation with its discomforts, risks, expenses, and time away from work.

This might also be unfortunate for the attending physician as it raises the possibility of a damaging law suit.

Measures to prevent this type of calculus formation are described.

FACTORS INFLUENCING THE MORTALITY AND MORBIDITY OF TRANSURETHRAL PROSTATECTOMY: A STUDY OF 2,015 CASES

H. LOGAN HOLTGREWE AND WILLIAM L. VALK

From the Department of Urology, Kansas University Medical Center, Kansas City, Kans. and the Veterans Administration Hospital, Kansas City, Mo.

The purpose of this study was to analyze the results of 5½ years of experience with transurethral prostatectomy. Chief interest was focused on complications of the procedure and on the assessment of those factors which influence mortality and morbidity of the operation. Two thousand fifteen consecutive transurethral prostatectomies were reviewed. These were operations performed by both staff and resident physicians. The scope of the study was confined to those postoperative deaths and complications occurring during the patient's hospital course. Longer term complications arising after the patient's discharge are not included.

The 2,015 operations were primarily performed for benign prostatic hypertrophy, vesical neck contracture and carcinoma of the prostate (table 1). Thirty-one miscellaneous diseases represented the remaining conditions requiring transurethral resection.

PROCEDURE

Two thousand fifteen consecutive transurethral prostatectomies were studied constituting all such operations performed at the Kansas University Medical Center and the affiliated Kansas City, Missouri, Veterans Administration Hospital over a 5½ year period from January 1955 through June 1960. Charts of all 2,015 cases were reviewed by a single investigator in an attempt to provide the greatest possible accuracy as well as uniformity of interpretation. The data from each case were coded and punched onto an IBM card and analyzed in the Data Processing Center of the Kansas University Medical Center.

TECHNIQUE OF OPERATION

Low spinal anesthesia was used in all cases unless medically contraindicated, and the dorsal lithotomy position was routinely employed. All resections were performed with either the Nesbit or Iglesias resectoscope. Irrigation fluid for all cases was distilled water with 1.1 per cent glycine.[1] The technique of prostatectomy performed was as described by Nesbit bringing about complete excision of the prostatic adenoma exposing the fibers of the surgical capsule throughout the entirety of the prostatic fossa.[2] External perineal urethrotomy was performed in cases where the resecting instrument was not commodiously accepted by the urethra and was carried out in 464 or 23 per cent of the cases studied. Blood was given during and following surgery in amounts commensurate to the losses sustained. Seven hundred thirty-eight patients or 37 per cent of the entire series received one or more units of blood in transfusion. Following removal of the resecting instrument, a size 24 or 26F Foley urethral catheter was left indwelling and was not irrigated unless its patency was compromised. When performed, the catheter was inserted by way of the external perineal urethrotomy. Patients were routinely placed on sulfisoxazole for the duration of their hospital convalescence unless complications prompted alteration. The catheter was removed on the third to the fifth postoperatve day depending upon the patient's postoperative course. Hospital discharge was on the seventh to ninth postoperative day. No other medications were routinely given aside from those for sedation.

MORTALITY

Any death occurring during or following operation prior to the patient's discharge from the hospital was considered as a mortality of surgery regardless of its cause. Fifty-one deaths occurred in the 2,015 cases for a mortality rate of 2.5 per cent. Table 2 shows the causes of death in order of decreasing frequency. Of the 18 deaths due to myocardial infarctions, one occurred in the

[1] Nesbit, R. M. and Glickman, S. J.: The use of glycine solutions as an irrigating medium during transurethral resection. J. Urol., **59**: 1212–1216, 1948.

[2] Nesbit, R. M.: Transurethral Prostatectomy. Springfield, Ill.: Charles C. Thomas, 1943.

TABLE 1. *Disease conditions necessitating 2,015 transurethral prostatectomies*

Disease Condition	Number of Cases	% of Total
Benign prostatic hypertrophy	1408	70
Vesical neck contracture	270	13
Carcinoma of the prostate	306	15
Neurological conditions	20	1
Bladder tumors metastatic to prostate	9	.5
Sarcoma	2	.1

TABLE 2. *Causes of death, 2,015 transurethral prostatectomies*

Cause of Death	Number	% Occurrence
Myocardial infarction	18	.9
Pulmonary embolus	10	.5
Cerebral vascular accident	5	.2
Pneumonia	5	.2
Pyelonephritis and sepsis	4	.2
Hemorrhage	3	.1
Acute renal failure	3	.1
Ruptured abdominal aneurysm	2	.1
Mesenteric artery thrombosis	1	.05

operating room and three on the day of operation. Of these four, none was associated with operative hypotension or unusual bleeding. The remaining infarctions occurred after the day of surgery. In all 10 cases of fatal pulmonary emboli, death was sudden and unassociated with previously suspected thrombophlebitis or phlebothrombosis. Of the 3 deaths due to operative hemorrhage, two were due to uncontrollable fibrinolytic reactions. Two of the 3 patients who died of acute renal failure displayed nitrogen retention at the time of admission to the hospital. None of the 3 cases was associated with detectable hemolysis. Dissection and rupture of an abdominal aneurysm resulted in the death of 2 patients. It is interesting to note that in both cases the lesion was known to exist preoperatively and that the dissection of the aneurysm began while the patient was on the operating table. Since the placement of the patient in the dorsal lithotomy position possibly precipitated these situations, we now consider an abdominal aneurysm a contraindication to the use of this position.

TABLE 3. *Nonfatal complications of 2,015 transurethral prostatectomies*

Complication	Number	% Occurrence
Epididymitis	120	6.0
Secondary resection	68	3.4
Pneumonia	25	1.3
Pyelonephritis	23	1.1
Extravasation	23	1.1
Non-specific sepsis	17	.8
Ileus	16	.8
Thrombophlebitis	15	.7
Uremia	14	.7
Idiopathic mental confusion	11	.5
Hemostatic procedure	11	.5
Fluid absorption toxicity	9	.4
Pulmonary edema in operating room	8	.4
Pulmonary embolus	7	.3
Shock in operating room	6	.3
Electrolyte imbalance	6	.3
Fibrinolysis	6	.3
Myocardial infarction	5	.2
Cerebral vascular accident	4	.2
Bleeding peptic ulcer	4	.2
Acute renal failure	2	.1
Septicemic shock	1	.05
Arterial embolus	1	.05

MORBIDITY

In the entire series, 18 per cent of the 2,015 cases experienced some type of nonfatal complication in addition to the 2.5 per cent who died, thus leaving 79.5 per cent of the patients who recovered without event. Table 3 lists the encountered non-fatal complications in order of decreasing frequency. Epididymitis was the most common postoperative complication and represented nearly half of all morbidity seen. Secondary resections necessitated by residual tissue, which was left at the time of the initial operation and which blocked proper voiding, were performed in 68 cases. Fever above 102F, chills, flank pain and tenderness with a leukocyte count above 15,000 wbc/mm.^{3} on two consecutive days were the arbitrarily established criteria to be met before a patient was placed in table 3 as having had pyelonephritis. Cases of upper tract sepsis with lesser symptoms doubtless existed and were either included as non-specific sepsis or if afebrile, went undetected. Patients who had an elevation of temperature over 100F after the third postoperative day without any demonstrable cause were termed as having non-specific sepsis.

The criteria for postoperative uremia were a postoperative rise of blood urea nitrogen above 23 mg. per cent, non-protein nitrogen above 40 mg. per cent or creatinine above 2.0 mg. per cent where these tests were normal preoperatively, or a 50 per cent increase if elevated preoperatively. Postoperative nitrogen and creatinine levels were not routinely obtained, and were determined only when the patient's clinical picture suggested the possibility of renal insufficiency. Therefore, asymptomatic rises in these levels would have gone undetermined.

Severe confusion and disorientation postoperatively in the absence of any abnormality of renal function, electrolytes, or central nervous system were seen in 11 patients. Although all subsequently cleared, they were considered to have had an operative complication and were listed in table 3 as idiopathic mental confusion.

Eleven patients were returned to the operating room for hemostasis. In all cases stasis was accomplished by electrocoagulation using the resectoscope and suprapubic prostatic packing was never required.

Routine serum sodium determinations were not obtained postoperatively and were ordered in the recovery room only when fluid absorption toxicity was suggested by the patient's clinical deterioration. A reduction of sodium below 125 meq/L was the arbitrary criterion for inclusion under this complication in table 3. Nine patients displayed this degree of hemodilution.

Fibrinolysis was seen in 6 cases within the series. Table 4 shows the occurrence of this complication with relation to benign prostatic hypertrophy, vesical neck contracture and carcinoma. Two of the 6 cases resisted all therapeutic efforts and ended in death.

Not a single complication was attributable to an external perineal urethrotomy. No complications occurred during hospitalization secondary to blood transfusions with the exception of several mild urticarial reactions.

TABLE 4. *Occurrence of fibrinolysis with various disease conditions*

Disease Condition	Number	Cases	% Occurrence
Benign prostatic hypertrophy	4	1408	0.3
Vesical neck contracture	1	270	0.3
Carcinoma of prostate	1	306	0.3
Entire series	6	2015	0.3

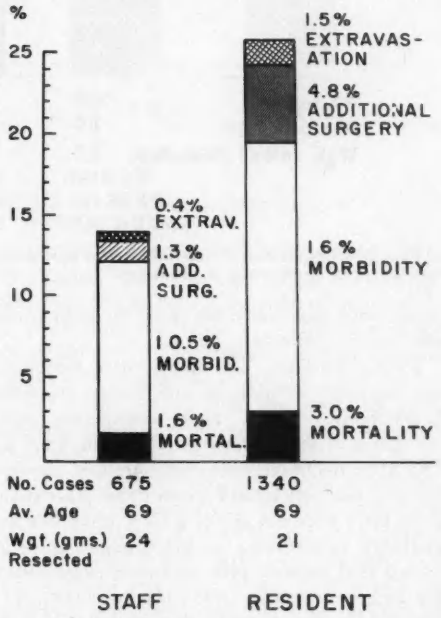


FIG. 1. Comparison of private and resident mortality and complications in entire series of 2,015 transurethral prostatectomies.

FACTORS INFLUENCING MORTALITY AND MORBIDITY

The aforementioned tables list the causes of death and all the non-fatal postoperative complications encountered in this series. With these as a background, a study was made to determine the influence of various factors upon the mortality and morbidity of the operation. Each of these factors will be dealt with separately.

Private versus clinic patients. The over-all mortality rate, morbidity rate, occurrence of extravasation and the necessity for secondary surgery for private and clinic patients are shown in figure 1. Both mortality and morbidity were noted to be lower in the private patients as was the necessity for secondary operative procedures for either hemostasis or residual prostatic tissue. Clinic patients were returned to the operating room nearly four times as often as those of the private staff. The occurrence of urinary extravasation at the time of surgery was also higher when the operation was done by the resident surgeon. It is interesting to note that the mean age and the average amount of tissue re-

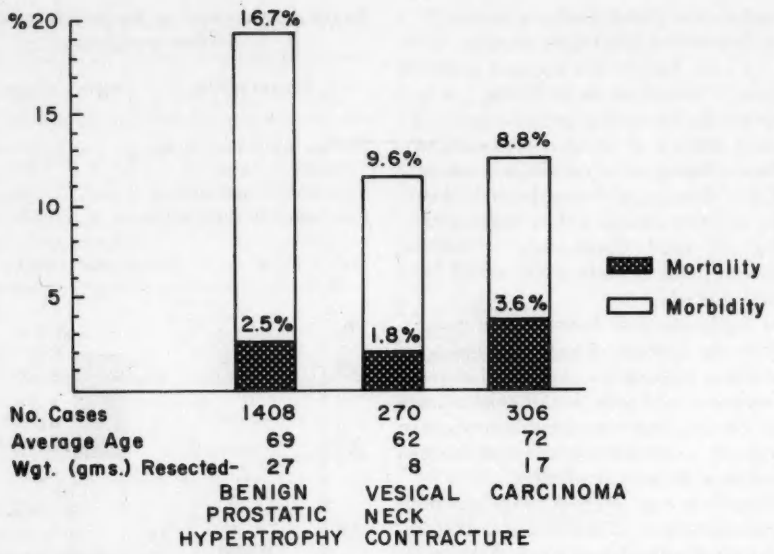


FIG. 2. Comparison of mortality and morbidity of benign prostatic hypertrophy, vesical neck contracture and carcinoma of prostate.

sected were essentially the same for both clinic and private patients.

Disease condition. The comparative mortality and morbidity of patients with benign prostatic hypertrophy, vesical neck contracture and carcinoma of the prostate are shown in figure 2. The 31 patients on whom transurethral prostatectomy was performed for conditions other than these three were not depicted since there was no mortality encountered in the group. Figure 2 reveals that patients with carcinoma experienced the highest mortality rate. The morbidity depicted in figure 2, as well as in figures 3, 4, 5, 6, 7 and 8, does not include secondary resections or extravasations. Morbidity was greatest in patients with benign prostatic hypertrophy and the incidence of all complications was lowest in patients with vesical neck contracture.

Age. The effect of age is depicted in figure 3. All 2,015 cases are contained in this table regardless of the patient's diagnosis or hospital classification and as seen, the average weight of tissue resected increased slightly with advancing age. Mortality remained low until the eighth decade of life when it underwent an abrupt increase to 4.0 per cent followed by an increase to 6.7 per cent for patients 80 years of age and over. The series contained 13 patients 90 years of age or over of whom three died following surgery. With so few cases it is impractical to speak of mortality in terms of per cent but the ratio is, indeed, sobering. The morbidity rate seems less affected with the advance of age and shows little alteration with increasing longevity.

Gland size. The relationship between gland size and mortality and morbidity is shown in figure 4. This figure depicts all cases in the series regardless of disease or classification except 24 cases in which the prostatectomy was deliberately accomplished in two stages several days apart. These two stage procedures will be dealt with separately. The mortality rate for single stage transurethral resections for glands under 40 gm. was 2.4 per cent while the rate for single transurethral resections for glands over 40 gm. was 2.9 per cent. Morbidity rates for the two groups were essentially the same. Thirty-three patients in the series had over 80 gm. resected at a single procedure. Of these, two died postoperatively, a mortality rate of 6.0 per cent. However, the small number of cases makes the figure inconclusive.

Operative time. Many urologists hold to the traditional concept of limiting resecting time during transurethral resection to 1 hour since it is their belief that extending the operative period beyond this results in increased hazards to the patient. This policy has not been rigidly subscribed to at this institution and many cases in

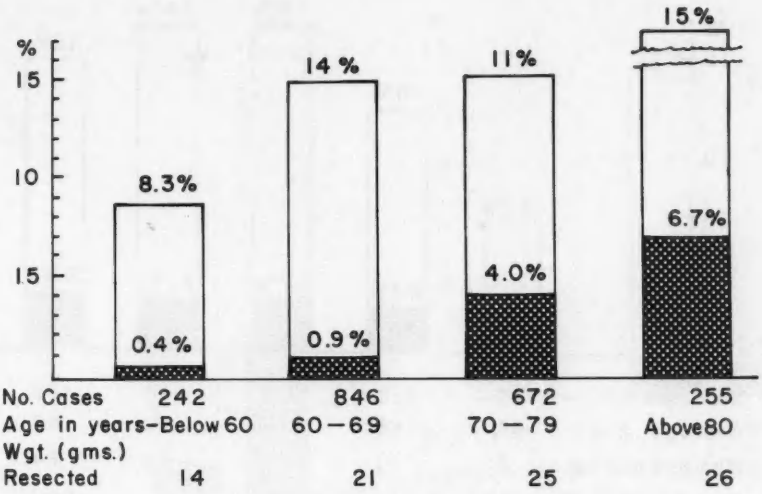


FIG. 3. Effect of age on mortality and morbidity of transurethral prostatectomy

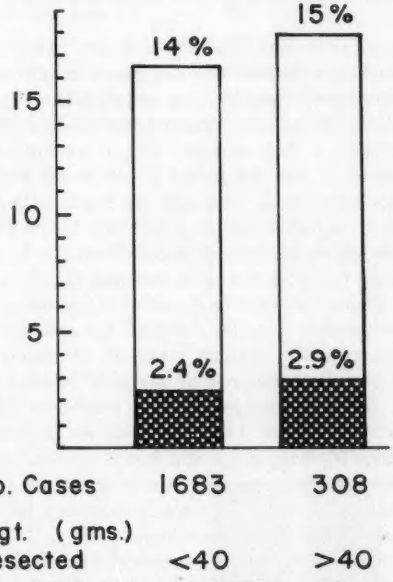


FIG. 4. Effect of gland size on mortality and morbidity of transurethral prostatectomy.

this series, especially those done by resident urologists, went well beyond this time interval. Provided that the patient was tolerating the procedure, our policy has been to resect until completed.

The duration of operation was coded to fall into one of five categories: 1 to 30 minutes, 30 to 60 minutes, 60 to 90 minutes, 90 to 120 minutes, and over 120 minutes. The determination as to operative time was made by examination of the anesthetist's record and includes the time elapsing between the beginning of draping until the removal of the patient from the operating table. Therefore, it is not synonymous with resecting time but includes draping, vasectomy (when done), perineal urethrotomy (when indicated), cystoscopy, panendoscopy, and associated endoscopic procedures such as bladder stone extraction when these were done concomitantly with transurethral resection. Junior resectionists are routinely supervised and the time required for endoscopic evaluation of their work by consultants also accounted for lengthening of operative time.

Figure 5 contains all cases in the series with the exception of the 24 patients done in two stages and shows surprisingly little increase in mortality and morbidity as operating time lengthens despite the fact that significantly larger amounts of tissue are being removed in the longer procedures.

The study of the effect of prolonged operative time was then carried further, since it was felt that the aged patient and the patient with disarranged renal function might tolerate an extended procedure poorly. The effect of prolonged operative time on three sub-groups of patients was ascertained: on those patients of all ages dis-

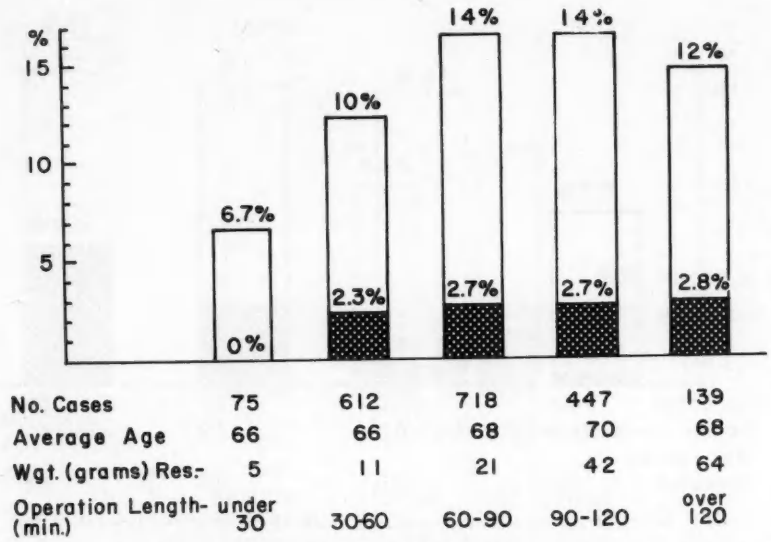


FIG. 5. Effect of operative time on mortality and morbidity of transurethral prostatectomy

playing impaired renal function on admission as reflected by nitrogen retention, those patients with apparent normal renal function over 80 years of age, and those patients with apparent normal renal function under 80 years of age.

The figure of 90 minutes' operative time was selected as the division point in the study of these three groups since it was felt that in the majority of cases this interval provided between an hour and an hour and a quarter of resecting time.

One hundred forty-five patients at the time of their admission displayed evidence of renal abnormality as reflected by elevations of non-protein nitrogen, blood urea nitrogen or serum creatinine. During the 5½ years under study, each of the foregoing was variably used as the routine screening test for renal function. Any elevation of this screening test at the time of admission placed the patient within this group irrespective of what subsequently happened to this determination after catheter drainage. A non-protein nitrogen of 40 mg. per cent or greater, or a blood urea nitrogen of 23 mg. per cent or greater, or a creatinine of 2.0 mg. per cent or over, was the criterion for inclusion. It is not within the intended scope of this paper to deal with the indications or contraindications of operation in the patient with nitrogen retention. However, the routine general policy of management in these cases was to place the patient on catheter drainage until the aforementioned tests reverted to normal or until such time as it was clinically felt the patient had reached a plateau of renal function. The latter time varied from days to months. The effect of prolonged operative time on this group is shown in figure 6. The mortality rate of patients whose operation was completed in under 90 minutes was 2.3 per cent, essentially the same as the overall series, while the patients subjected to longer procedures experienced a significant rise in mortality rate with the figure reaching 10 per cent.

Figure 7 deals with the effect of operative time on patients over 80 years of age and without demonstrable nitrogen retention on admission. It reveals no increase in mortality or morbidity in the group subjected to a procedure lasting over 90 minutes. The same study for all patients under 80 years of age and free of nitrogen retention on admission is shown in figure 8. Again, there is no noted increase in mortality or morbidity with longer procedures.

Preoperative acute pyelonephritis. Fifty-five patients were diagnosed as having acute pyelonephritis at the time of their admission on a basis of fever, chills, flank pain and tenderness, pyuria and a leukocyte count of over 15,000 wbc/mm³. All were subsequently treated with bed rest, catheter drainage, high fluid intake and appropriate antibacterial agents until considered quiescent at which time transurethral prostatectomy was performed. There was no hospital mortality in this group. Six experienced morbidity

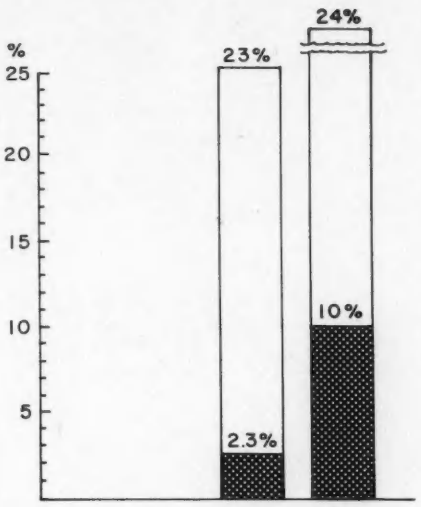


FIG. 6. Effect of prolonged operative time on patients with nitrogen retention at time of admission.

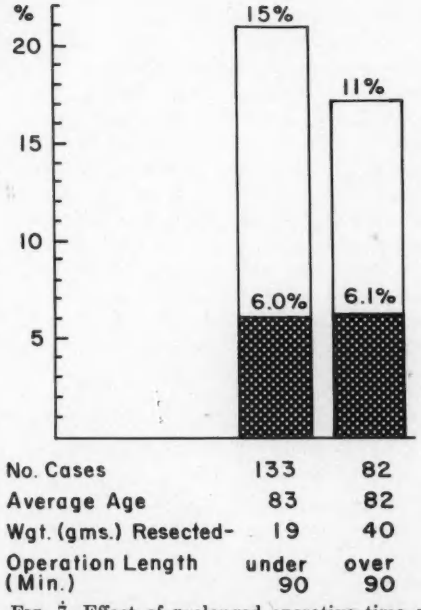


FIG. 7. Effect of prolonged operative time on patients with normal renal function over 80 years of age.

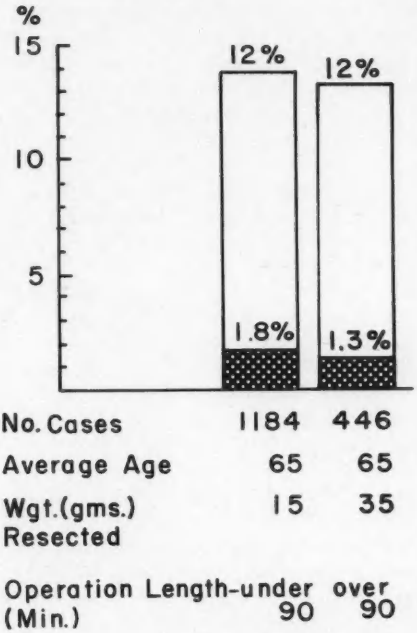


FIG. 8. Effect of prolonged operative time on patients with normal renal function under 80 years of age.

for a rate of 11 per cent. Only one had a postoperative recurrence of his renal sepsis and none experienced renal failure or septicemia. The group thus appeared to experience no exceptional mortality or morbidity.

Patients with a single kidney. Sixteen patients in the series had undergone previous nephrectomy for various reasons and came to transurethral prostatectomy with a single kidney. Of these, two displayed nitrogen retention on admission. None of the 16 died postoperatively. Epididymitis developed in three and acute pyelonephritis in one. The group, although small, seemed to tolerate the procedure without undue complications.

Operative extravasation. Twenty-three patients sustained extravasation at the time of operation for an occurrence rate of 1.1 per cent. Of these, four subsequently died affixing a mortality rate of 17.5 per cent to patients who experienced this complication. However, table 5 reveals that all 4 deaths occurred in those 12 patients in whom suprapubic cystotomy and drainage were delayed beyond 2 hours after the perforation. The 11 patients in whom drainage was effected in less

than 2 hours following surgery all recovered without incident or complication. It is thus seen that in those cases in which drainage was delayed over 2 hours, the mortality rate was four out of twelve. The morbidity was also profound in this group since five of the eight who survived experienced some major complication leaving but three of the original twelve who recuperated without incident. It is of interest to note that three of the 4 deaths in this group of extravasation were due to pulmonary emboli.

Vasectomy. The matter of epididymitis prophylaxis is only superficially dealt with in this study since it was not until the last 9 months under study that it was the policy of the service to perform any type of vas deferens interruption prior to surgery. The number of patients having procedures was, therefore, small and the results possibly inconclusive (table 6).

One thousand eight hundred twelve patients in the group had no procedure to interrupt the continuity of the vas deferens prior to transurethral resection. Of these, postoperative epididymitis developed in 111 or 6.1 per cent. Ninety-one patients in the series had vas deferens crushing with a Burdizzo clamp as previously described by Zufall.[3] Among these, epididymitis developed in 5.5 per cent virtually the same ratio as the untreated group. One hundred twelve patients of the series had vasectomy of which only one or 0.9 per cent experienced epididymitis. These figures suggest, at least in our hands, the superiority of vasectomy in the prevention of epididymitis, since the crushing of the vas deferens with the Burdizzo clamp proved of little benefit.

Preoperative epididymitis. Acute epididymitis was present in 40 patients at the time of their admission to the hospital. None of these had vasectomy at the time of their transurethral resection. Their postoperative course was not appreciably different from that of the whole study except that 5 patients experienced a postoperative recurrence of epididymitis in the same testicle. There was one death in the group, a mortality rate of 2.2 per cent. The morbidity rate of 27 per cent was distorted by the increased incidence of epididymitis due to the aforementioned recurrences.

Secondary resections. Secondary resection of residual prostatic tissue necessitated by poor postoperative voiding was performed in 68 patients, an occurrence rate of 3.4 per cent. None of these patients died, but their postoperative morbidity rate was significantly elevated to 19 per cent due to a 12 per cent incidence of epididymitis, nearly double that of the series as a whole. This would indicate the second procedure carried no untoward effect aside from doubling the likelihood of epididymitis.

[3] Zufall, R.: Burdizzo clamp to crush vas. J. Urol., **80:** 199–202, 1958.

TABLE 5. *Effect of delayed drainage and cystotomy after extravasation (23 cases in 2,015 operations, 1.1%)*

	Number	Mortalities	Morbidity
Drainage within two hours	11	0	0
Drainage after two hours	12	4	5

TABLE 6. *Effect of vas deferens manipulation in prevention of epididymitis*

	Number	Epididymitis	Occurrence
No procedure	1812	111	6.1%
Vas crushing	91	5	5.5%
Vasectomy	112	1	0.9%

Effect of previous transurethral surgery. Two hundred thirty-five patients or 11.6 per cent of the entire series gave a past history of having had one or more previous transurethral prostatectomies at the time of their admission. Two of these died postoperatively giving a group mortality rate of 1.4 per cent below that of the series as a whole. Morbidity was also significantly lower and occurred in only 7 per cent of the group. This lower figure was due to the fact that not a single case of epididymitis was seen in patients of this group. Apparently their previous surgery in some way protected them from subsequent epididymal infection.

Two stage resections. Due to difficulties encountered during their operation, 24 patients had deliberate completion of their prostatectomy at a second procedure. The reasons for inability to effect a complete resection at the initial operation were variable and included anesthetic inadequacy, deterioration of the patient's condition and discrepancy between gland size and resident resectionist proficiency. An average of 80 gm. was resected from each patient. Of the

24 in this group, two died postoperatively, for a mortality rate of 8.3 per cent, higher than the group as a whole but of questionable significance in view of the small number of cases.

DISCUSSION

It is clear that the resident surgeon encountered more complications and greater mortality than the attending staff. No attempt was made to evaluate the patient's general physical condition but it is nonetheless the impression of the authors that the group of clinic patients contained a much greater number of poor risk patients who on admission presented advanced and neglected physical disorders.

The 1.6 per cent mortality rate for private patients in this series corresponds to other series of private patients previously reported by O'Brien and associates,[4] Ray and associates,[5] and Bergman and associates.[6] Also, the 3.0 per cent mortality rate of resident cases compares with previous resident series published by Nesbit[2] and Creevy.[7]

The size of the prostate gland appeared to exert far less effect on mortality than did the patient's age. Again, these findings are in accord with those previously recorded by Bergman and associates[6] and O'Brien and associates.[4] The mortality rate of 2.9 per cent for patients with over 40 gm. resected approximates the mortality rates of 2.8 per cent and 2.9 per cent reported by Lee and associates[8] and Turner and associates[9] respectively in those authors' large series of perineal prostatectomies.

Special interest was devoted to operative time and its effect on mortality and morbidity since this is a subject about which there has been little recent work in the literature and yet about which there exists considerable tradition. Our study was made interesting by the presence within the series of a large number of operations done by residents, many of which were lengthy procedures lasting two hours or more. These cases provided an excellent opportunity to ascertain factually if long resections are associated with high complication rates. Prolonged operative time appeared to exert no pronounced undesirable effect on the patient's postoperative course unless he was a member of the group displaying nitrogen retention at the time of his admission.

As previously stated, any elevation of the admission renal function screening test placed a patient within this group irrespective of what subsequently happened to this determination on catheter drainage. All patients in this group came to surgery either having reverted to normal or after having been considered at a plateau of renal function after an interval of drainage. The fact that this group experienced a significantly higher mortality rate if subjected to a prolonged resection is presented merely as a documented observation. The authors defer any explanation of this observation since a more complete and detailed assessment of this problem is currently being made.

CONCLUSIONS AND SUMMARY

The mortality and morbidity of 2,015 consecutive transurethral prostatectomies have been studied and the effect of several factors on mortality and morbidity has been analyzed. From the foregoing, the authors feel three very important factors emerge:

First, current concepts of the importance of operative time perhaps need re-evaluation. From the results of this series, it appears that only those patients who display nitrogen retention on admission experience ill effects from a prolonged operative procedure. Even the patients over 80 years of age, if free of azotemia on admission, tolerate longer operations without significant harmful results. These findings suggest that the continued adherence to the traditional concept of a one-hour limit on resection time is unnecessary.

Secondly, there appears a profound increase in

[4] O'Brien, H. A., Mitchell, J. D., Jr. and St. Martin, E. C.: Transurethral resection of large prostates. J. Urol., **62:** 225–230, 1949.

[5] Ray, E. H.: Transurethral resection of the prostate. J. Urol., **69:** 407–410, 1953.

[6] Bergman, R. T., Turner, R., Barnes, R. W. and Hadley, H. L.: Comparative analysis of one thousand consecutive cases of transurethral prostatic resection. J. Urol., **74:** 533–545, 1955.

[7] Creevy, C. D.: Mortality of transurethral resection. J. Urol., **65:** 876–882, 1951.

[8] Lee, L. W., Malashock, E. M. and Davis, N. B.: Experience with transurethral resection and perineal prostatectomy in one clinic. J. Urol., **80:** 147–150, 1958.

[9] Turner, R. D. and Belt, E.: Results of 1,694 consecutive simple perineal prostatectomies. J. Urol., **77:** 853–863, 1957.

[10] Lynn, J. M. and Nesbit, R. M.: Influence of vasectomy upon incidence of epididymitis following transurethral prostatectomy. J. Urol., **59:** 72–75, 1948.

[11] Mortensen, H.: Morbidity after prostatectomy by transurethral resection. Med. J. Australia, **23:** 919–921, 1955.

mortality rate after the seventh decade of life. While such a relationship is not surprising, it strongly supports the principle of early elective prostatectomy once the symptoms of prostatism are established.

Thirdly, the importance of recognition and drainage of urinary extravasation within two hours is vividly shown since delay beyond this time is attended by a marked increase in mortality and morbidity.

TRANSRECTAL BIOPSY TO DETECT PROSTATIC CARCINOMA: A REVIEW AND REPORT OF 203 CASES

JOHN L. EMMETT, KENT W. BARBER, JR. AND RAYMOND J. JACKMAN

From the Sections of Urology, Surgery, and Proctology, Mayo Clinic, Rochester, Minn.

PART I. THE RATIONALE OF PROSTATIC BIOPSY

Prostatic biopsy has received much attention in recent urologic literature. Among the controversial issues being discussed is the relative accuracy of the various methods of biopsy. It seems worth while to stop and consider this problem objectively. Are standards available by which the accuracy of this diagnostic procedure can be determined? Are we able to truly assess the significance of so-called positive or negative biopsies in given situations, obtained by various methods?

This paper will not deal with the controversial problem of therapy. Familiarity with current thinking on this subject, however, is necessary before diagnostic biopsy can be placed in its proper perspective. The classic article of Whitmore is especially recommended as an excellent comprehensive survey of the subject. Other authors who have presented data pertinent to this subject include Barnes and Emery, Flocks, Culp, Greene and Simon, Hinman, 1948, Jewett 1958 and one of us (J. L. E.) and associates.

Incidence of carcinoma of the prostate in men 50 years of age and older. As a starting point for an evaluation of prostatic biopsy it should be helpful to be familiar with the incidence of carcinoma of the prostate in males 50 years of age or more.

Necropsy data: The most accurate information available comes from postmortem studies of series of more or less "unselected consecutive" cases using the step-section technique. The next best information comes from similar studies that employ only routine technique (from 1 to 10 blocks of tissue examined). When carcinoma was apparent clinically or grossly, the case was excluded from some of the studies. In most series, however, all cases have been included. If the malignant lesion could not be recognized clinically or grossly, but only on histologic section, the terms "latent" or "occult" carcinoma have been employed. A summary of the reported incidence encountered at necropsy is shown in table 1.

From this table it is obvious that the incidence of carcinoma increases in direct proportion to the thoroughness with which the prostate is examined. When the step-section technique was used, the average incidence appears to be approximately 24.0 per cent,* whereas if only random sections are examined it is approximately 13 per cent.

Clinical data: Finkle stated that of 10,673 cases of prostatic enlargement encountered at the Brady Urological Institute, Johns Hopkins Hospital prior to June 1950, 2304 (21.5 per cent) were diagnosed as carcinoma. Hugh Young (1950) stated that carcinoma was found in more than 20 per cent of the patients with urinary obstruction in the region of the prostate admitted to Brady Urological Institute.

Surgical data: General aspects.—Another method of estimating the incidence of prostatic carcinoma is on histologic examination of prostatic tissue removed at operation. Here again, the incidence varies according to 1) the type of surgical operation performed (open removal versus transurethral resection), 2) the thoroughness of the examination of tissue (step section versus random section in enucleated prostates and number of pieces examined after transurethral prostatic resection), and 3) whether or not carcinoma is evident clinically before operation.

Data on routine prostatic surgery regardless of the preoperative diagnosis: In 1911 Wilson and McGrath of the Mayo Clinic reported on a series of 468 prostates removed by suprapubic prostatectomy. Seventy-three (15.6 per cent) were found to be carcinomatous. Hunt, also of the Mayo Clinic, stated in 1924 that "Malignancy of the prostate comprises 15 per cent of the glandular lesions which require surgical treatment." Hugh Young (Johns Hopkins) reported in 1933 an 11 per cent incidence of carcinoma of 4295 prostatectomies. Treiger and associates, in 1948, reported the finding of carci-

* Luppi's figures are not included in this average as they appear to be completely at variance with all other studies.

TABLE 1. *Incidence of prostatic carcinoma reported in men 50 years or more of age as determined at necropsy*

Author	Year	Cases	
		Examined	Carcinoma, per cent
Cases studied by step-section technique			
Moore	1935	229	20.5
Walthard	1937	100	30.0*
Gaynor	1938	880	20.7
Kahler	1939	381	17.3
Baron and Angrist	1941	50	46.3
Oswald	1941	98	14.3†‡
Gil Vernet	1944	210	25.0*
Luppi	1947	85	3.6
Meyenburg and Cathomas	1948	100	23.0*†
Andrews	1949	99	16.0
Horstmann	1952	106	15.0†
Edwards and associates	1953	150	22.0†
Franks	1954	178	37.6
Cases studied by routine (random-section) technique			
Muir	1934	54	13
Rich	1935	292	14
Baron and Angrist	1941	364	14.8
Gloggengiesser	1958–1959	200	12.0

* Patients 40 years of age or more.

† Corrected to exclude patients less than 50 years of age.

‡ Cases of clinically detectable carcinoma were excluded from study.

noma in 12.6 per cent of 108 prostates removed suprapubically. Harrison and Poutasse reported 200 consecutive cases of operations on the prostate for urinary obstruction. Various types of operation were performed: suprapubic, retropubic, perineal and transurethral resection. Carcinoma was found in 37 (18.5 per cent). Bergman and associates found carcinoma in 15.7 per cent of 1000 consecutive cases in which transurethral prostatic resection was performed. Holtgrewe and Valk in a series of 2015 transurethral prostatectomies found carcinoma in 306 (15 per cent). At the Mayo Clinic during the past 25 years, more than 25,000 transurethral prostatic resections have been done, and the incidence of carcinoma of the prostate in these cases has been approximately 13.0 per cent. For all of the histologic examinations in the studies mentioned thus far, the routine (random-section) technique was employed.

Data on open operation for presumably benign prostatic hyperplasia: The incidence of carcinoma found in prostates removed by open operation in cases in which the preoperative clinical diagnosis was benign prostatic hyperplasia is given in table 2. The great variation in incidence (4.6 to 29.4 per cent) seems to result from such variables as thoroughness of the preoperative examination and method of histologic examination of the removed prostate (step-section or random-section technique).

Data on transurethral resection for presumably benign hyperplasia: Greene and Simon,

TABLE 2. *Carcinoma found at open prostatectomy after preoperative diagnosis of benign prostatic hyperplasia*

Author*	Year	Cases		Method of histologic examination
		Total	Carcinomas, per cent	
Albarran and Hallé	1900	100	14.0	Routine
Wade	1914	130†‡	7.7	Routine
Swan	1923	28	14.0	Routine
Hunt (Mayo Clinic)	1930	Not stated	6.0	Routine
Ferguson	1933	1426	12.8	Routine
Myers	1937	75	29.4	Routine
Bibus	1937	430	4.6	Step-section
Smith and Woodruff	1950		6–10	Routine
Labess	1952	98	9.2	Routine
Allemann	1952	280	5.0	Routine
Finkle (Johns Hopkins)	1954	141§	14.1	Routine

* Palomo stated that in 21 per cent of a series of 276 surgical cases of carcinoma of the prostate the preoperative diagnosis was benign prostatic hyperplasia.

† Figures corrected to exclude cases in which clinical diagnosis of carcinoma was made before operation or necropsy.

‡ Necropsy finding when patients died either after operation or before operation could be performed for prostatism.

§ Patients with prostatic calculi.

in 1955, found occult carcinoma in 4 per cent of 2090 cases in which transurethral resections were done for benign hyperplasia at the Mayo Clinic. The incidence is low no doubt because of the rigid selection of cases. In addition to stipulating benign consistency on digital-rectal palpation, they also excluded any case in which the cystoscopic appearance or the consistency of the gland during cutting with the cold knife resectoscope suggested carcinoma.

Site of origin of prostatic carcinoma. When the accuracy of a prostatic biopsy is being evaluated, knowledge of the location in the prostate where carcinoma most frequently originates should be helpful. Is early carcinoma located in such a position that it can be palpated readily on digital-rectal examination or is palpable carcinoma a late stage of the disease?

Evidence for and against a posterior lobe of the prostate: Since the article by Geraghty in 1922, it has been taught that carcinoma originates most frequently in the "posterior lobe" of the prostate. Inasmuch as there is considerable difference of opinion as to whether or not a posterior lobe actually exists, a brief discussion of this subject seems indicated herewith. For details the interested reader is referred especially to the excellent summaries of this subject in the articles by Le Duc, Swyer, and Franks 1954 (A).

Lowsley (1912) on the basis of a detailed embryologic study first described a posterior lobe. He described it as an independent structure made up of tubules (glands) which originate from the floor of the prostatic urethra below (caudad to) the openings of the ejaculatory ducts. The tubules grow cephalad behind the ejaculatory ducts. Lowsley defined the posterior lobe in the adult as that part of the prostate which lies dorsal to the ejaculatory ducts above (cephalad to) their entrance into the verumontanum, and dorsal to the urethra below (caudad to) this point. He explained that this is the part of the prostate which is felt per rectum. This embryologic concept has been supported by Johnson, and its physiologic concept has been supported by Huggins and Webster in their study of the response of prostatic epithelium to estrogens. Anatomic support of this concept, however, has been lacking according to LeDuc writing in 1939, Swyer in 1944 and Franks in 1954 (A).

At present the most widely accepted concept of the tubular (glandular) structure of the prostate is its division into an inner and outer group of glands. This view was favored by Jores writing in 1894, Albarran and Motz in 1902, Motz and Perearnau in 1905, Adrion in 1922, Jacoby in 1923, LeDuc in 1939 and Franks in 1954 (A). The inner group of glands (O.T. central, periurethral, accessory, mucosal, submucosal) is considered to be the site of origin of benign prostatic hyperplasia. The outer group (O.T. true prostatic glands) is considered to be the most common site of origin of carcinoma by Edwards and associates (1953) and Franks (1954, A).

Necropsy data: In the necropsy studies summarized in table 1, Rich noted a "decided tendency" for the early tumors to be situated either laterally or posteriorly in the tissue near the capsule of the gland; Moore found that of the lesions which were small enough so that the point of origin could be determined 73.5 per cent arose in the posterior lobe, and multiple sites of origin were common. Gaynor found approximately 60 per cent in the "posterior lobe," and multiple sites were not uncommon. Andrews found the lesions located most commonly "beneath the capsule of the posterior lobe." Edwards and associates of Winnipeg in 1953 stated that of their 29 "latent" carcinomas, 27 were small enough that the site of origin could be determined. There were 41 individual foci of malignancy in these 27 cases. Thirty-six of these were predominantly subcapsular in distribution, which they thought would correspond to the distribution of the outer (peripheral) tubules. Of the 41, approximately half (21) were found in the area corresponding to the posterior lobe, 14 were in the lateral lobe, and six were anterior to the urethra.

Franks of London, in 1954 (A), found most of his latent carcinomas just beneath the capsule in the posterolateral angles of the gland. Infiltration of the capsule was common even in small tumors (52 of 69 cases). Invasion of lymphatics and blood vessels was also common even with small lesions. He considered that almost all had originated in the outer (peripheral) glands. He emphasized the circumferential spread of the tumors, stating that serial sections show that many of these separate tumors or nodules are connected in this way. We concluded that "prostatic tumors may have already spread beyond

the confines of the gland long before they are clinically diagnosable."

Baron and Angrist reported that in 23 cases of carcinoma the location of the lesion was in the lateral lobes in 9 cases and the posterior lobe in four, and in 10 cases it was either too large to allow determination of the site or occurred at the junction of the lateral and posterior lobes, invading each. Kahler's studies led him to state that carcinoma of the prostate does not arise predominantly from any one lobe of the gland. His findings are similar to those of Franks in that he also found a high incidence of early invasion of the capsule and lymph nodes.

Hugh Young always maintained that the overwhelming majority of carcinomas of the prostate originated in the posterior lobe and rarely invaded the encapsulated, benign, adenomatous hyperplastic tissue of the lateral and median lobes. He was so convinced that carcinoma did not originate in the lateral or median lobes that he called attention to the case reported by Shaw *as the only example of carcinoma discovered solely within an encapsulated adenomatous lobe* in 2500 prostatectomies done for benign hyperplasia at the Brady Urological Institute.

Relationship of latent (occult) to manifest (clinical) carcinoma of the prostate. "Latent" and "occult" are terms used rather loosely to describe malignant lesions of the prostate that are not readily demonstrable clinically. Some authors use the terms in a more limited sense to indicate that the lesion cannot be detected grossly, on clinical examination or at operation or necropsy when the prostate is in the hand for palpation and visual inspection. These terms are in contradistinction to the terms "manifest" or "clinical" which designate a lesion that can be readily recognized as a carcinoma clinically or on gross palpation or inspection.

It has been suggested that the palpable carcinomatous nodule in man represents a different disease from that represented by the non-palpable (occult) carcinoma. In 1954 (A) Hudson and associates, after extensive study, concluded that latent and manifest carcinomas are not basically different. They also stated that findings on digital-rectal examination are not related to the microscopic findings of open perineal biopsy or total extirpation of the gland. They expressed the view that induration is simply a late manifestation of the disease.

Hinman's interpretation (1948) of Moore's study is that regardless of the site of origin in the prostate the carcinoma spreads distally (caudad) beneath the capsule, so that no matter what portion of the gland is first involved the posterior portion is involved before the capsule is breached. In his opinion this is the reason that most of the early authors in America, such as Geraghty in 1922, concluded that all cancer of the prostate originated in the so-called posterior lobe. It is Hinman's view that they merely saw a later stage in the surgical specimen than Kahler and others have observed in necropsy material. That the palpable nodule does not represent a particularly early stage of the disease seems a reasonable assumption (Whitmore).

From necropsy studies one gains the impression that there is probably no basic difference between occult carcinoma and the palpable nodule. Franks (1954, B) stated that latent carcinoma has the morphologic and some of the histologic characteristics of true malignancy (that is, infiltration) but that it "lacks the capacity for rapid growth."

Hirst and Bergman, using an ingenious method of comparing occult and clinical carcinoma, compared the incidence of carcinoma of the prostate found at necropsy using routine technique with the incidence found in cases examined by the step-section technique. They grouped the cases according to age of the patient by decades and charted their findings on a probit graph. In this manner they demonstrated to their satisfaction a period of approximately 20 years between the onset of occult carcinoma which can be demonstrated only by the refined step-section histologic technique and clinical carcinoma when the tumor reaches sufficient size to make the diagnosis evident on 1) a digital-rectal palpation, 2) examination using routine technique or 3) demonstration of metastasis.

Baker suggested that the factor responsible for continued inactivity of small or occult prostatic carcinoma may be the concentration of the physiologic estrogen in serum or perhaps the decreased concentration of testosterone in serum. This concept of the relative slow growth of carcinoma of the prostate is supported by Barnes and Emery who asserted that less than 3 per cent of patients who have early, clinically demonstrable carcinoma of the prostate will die within 5 years of the time the diagnosis is made.

As a result of a study of occult carcinoma encountered during transurethral resection in

more than 2000 cases at the Mayo Clinic, Greene and Simon mentioned the possibility of a difference in the character and potential of occult and clinical carcinoma. They recalled the study of Dossot and wondered whether occult carcinoma in some cases might originate in the periurethral glands located near the urethral lumen in contrast to clinical or manifest carcinoma whose origin is thought to be in the peripheral glands of the prostate. Evidence to support this assumption is not available as yet.

Prostatic biopsy. "Open" perineal biopsy:—Perineal biopsy with the prostate surgically exposed has long been considered the most nearly accurate form of prostatic biopsy. To evaluate this procedure, one must consider the type of case and reason for the biopsy. Hudson and associates in 1955 showed that, if routine open perineal biopsy is performed on an essentially consecutive series of aging males regardless of the consistency of the gland on digital-rectal palpation, carcinoma will be found in approximately 11 per cent. If this incidence is compared to that derived from the postmortem studies available (a 24 per cent incidence of carcinoma on use of the step-section technique), one must conclude that such biopsy is less than 50 per cent accurate, according to Hinman (1955). This seems reasonable in view of the fact that the surgeon has no idea of the part of the gland involved. Therefore, biopsy may be considered only a "random sampling" as far as the remainder of the prostate is concerned. On the other hand, if perineal biopsy is done to sample a palpable nodule suspected of being malignant, a different problem is posed. If Hudson, Hinman and Franks are correct in their assumptions that this constitutes a "fairly late stage of the disease," then the incidence of carcinoma should be much higher and the degree of accuracy greater because 1) the nodule pin points the area most likely to be involved with carcinoma, and 2) the chance of a substantial segment of the prostate being involved with tumor is considerable.

Incidence of carcinoma in the palpable prostatic nodule: The finding of malignancy in the palpable prostatic nodule depends on such factors as the threshold of suspicion and selection of cases for biopsy. If the physician suspects most palpable nodules and performs biopsy, the incidence of malignancy in his series of cases in which biopsy is performed will be considerably lower than that of the physician who biopsies only those that he is reasonably certain are neoplastic. Thus Jewett, in 1954, found carcinoma in 45 per cent of 91 such cases in which open perineal biopsy was performed; Higbee, in 1953, in 86 per cent; Kaufman, Rosenthal and Goodwin (1956) in 74 per cent; Webb and Smith, in 1956, in 75 per cent; Culp, in 1959, in 77 per cent and Bianchi, in 1956, in 89 per cent. A high incidence of positive biopsies means careful selection of cases; it also may mean that some patients in whom carcinoma is present may be denied biopsy.

Accuracy of open perineal biopsy: The accuracy of open perineal biopsy for palpable nodules can be evaluated only if the prostate is rendered available for microscopic examination by surgical removal regardless of the biopsy findings and if histologic examination of the prostate is performed with the step-section technique. Few if any such studies are available. Using the routine random-section technique, Colby, in 1953, reported an accuracy of 92 per cent in 36 cases; Webb and Smith, in 1956, an accuracy of 93 per cent in 43 cases. Culp, in 1959, proceeded with radical prostatectomy only when carcinoma was found on biopsy. In all of his cases in which biopsy showed carcinoma, the diagnosis was verified by microscopic examination of the removed prostate. The accuracy of the negative biopsies was not routinely checked by simple enucleation; this was done only in those cases in which obstructive urinary symptoms were present. There is a growing feeling in the profession that radical prostatectomy should not be done unless the diagnosis of carcinoma has been proved unequivocally by tissue biopsy. As Culp and McDonald pointed out, at our clinic we can rely on fresh frozen sections because our pathologists are experienced and favorably disposed to this type of procedure. In other centers, however, urologists often prefer to close the perineal wound after biopsy and wait for 2 to 3 days until fixed sections have been studied. If the report is positive for carcinoma, the perineal wound is reopened and radical prostatectomy is performed.

As an example of the diagnostic errors that may occur if radical procedures are performed without preliminary biopsy, the report of Memmelaar (1949) may be mentioned. Three of nine prostates removed by radical (total) retropubic prostatectomies on the basis of a preoperative

clinical diagnosis of carcinoma, were found to be benign when the prostate was examined microscopically.

Transurethral biopsy: Transurethral biopsy is generally considered an inadequate method. Hudson and associates, in 1954(B), compared it with open perineal biopsy in 59 consecutive cases. Preliminary transurethral biopsy detected carcinoma in only eight (50 per cent) of their 16 cases in which carcinoma was found by open perineal biopsy. Tissue removed in the course of complete transurethral resection will have a greater chance of exhibiting malignant tissue if any is present, as the bulk of the prostate must be removed before the resectoscope gets down to the portion of the gland near the capsule.

Perineal needle biopsy: What has been said about the limitations of prostatic biopsy in general is even more applicable to the needle or punch method of biopsy. In cases in which no nodule is palpable to guide the needle, only a minute portion of the total prostatic volume is sampled. If a nodule is present, some skill is required to be sure that the point of the needle is in the proper position in the nodule; furthermore, the core of tissue removed is very small. The considerable difference of opinion concerning the reliability of perineal needle biopsy is illustrated by the following opinions:

1) Hudson and associates, in 1955, compared perineal needle biopsy with open perineal biopsy in unselected cases, regardless of the contour or consistency of the prostate on digital rectal palpation. They stated it was either inadequate or missed the carcinoma in 32 per cent of cases.

2) Kaufman, Rosenthal and Goodwin, in 1956, compared needle biopsy with open perineal biopsy and "positive" biopsy by transurethral resection in patients with "suspicious prostates," and found it to be 71 per cent "accurate."

3) Comparison with surgically removed prostates showed that needle biopsy was accurate in 73 per cent of Colby's cases; in 94.6 per cent of Bianchi's; in 86 per cent of Peirson and Nickerson's and in 96 per cent of Rinker and Shuman's.

Several workers have expressed favorable opinions concerning perineal needle biopsy; among them may be mentioned Needell, Slotkin, Mitchell and Friedmann, Peck, Spring and Alden, and Veenema. Clarke, Leadbetter and Campbell and Goldman and Samellas have called attention to the occasional complication of implanting carcinoma cells along the needle tract in the perineal tissue.

Transrectal biopsy: Astraldi of Argentina, in 1937, was the first to report a series of cases of transrectal biopsy of the prostate. To Grabstald and Elliott, however, must be given the credit for the widespread use of transrectal biopsy of the prostate in this country. For years the procedure was shunned by the profession because of the fear of infection, or fistula, or both. There are now sufficient cases reported in the literature to indicate that the procedure is safe and is essentially devoid of serious complications. As Grabstald pointed out, it provides an easier, more direct, and accurate method of obtaining specimens from selected palpable portions of the prostate gland than does the perineal needle biopsy. Whereas it is somewhat difficult and requires considerable experience to introduce accurately the tip of a needle through a relatively thick perineum into a prostatic nodule guided by a finger in the rectum, it requires less experience and special skill to insert it through the readily accessible rectal mucosa into a nodule that lies immediately beneath the rectal mucosa. It is also easier to approach the nodule perpendicularly than tangentially which is so often the case with perineal needle biopsy. Also, if a larger specimen is desired, it is safe to expose the nodule in the prostate through a small incision in the rectal wall and remove a piece of prostatic tissue directly with a sharp pituitary rongeur or other suitable forceps. However, the procedure is not recommended if radical perineal prostatectomy is being considered as the difficulty of the surgical dissection may increase considerably.

To the present writing, reports on more than 500 cases of transrectal biopsy have appeared in the literature as follows: Astraldi, in 1937, more than 100 cases; Grabstald in 1954, more than 100 cases (he has not given the number of cases since this report); Pearlman, in 1955, 40 cases; Emanuel and Foote in 1957, 44 cases; Graham in 1958, 54 cases; Barnes and Emery, in 1959, 20 cases and Daves, Tomskey and Cohen, in 1961, 160 cases. No substantial series of cases has been compared with open perineal biopsy or enucleation of the prostate, as yet, because biopsy usually is not performed in cases in which possible radical prostatectomy is being considered for fear of increasing the difficulty of the operative procedure. Also, in cases in which either simple enucleation or transurethral resection must be done regardless of diagnosis to relieve urinary obstruction, the urologist is

usually content to await the pathologic report of the tissue removed at operation. Graham stated that it was 90 per cent accurate "compared to transurethral resection," and "as accurate" or "more accurate" than perineal needle biopsy because of easier accessibility of the prostate to the needle or biopsy forceps.

General appraisal of prostatic biopsy. From the foregoing discussion prostatic biopsy obviously is not a simple straightforward diagnostic procedure which can provide computer machine answers. Each urologist must evaluate for himself such factors as the comparative clinical importance of nodular and occult or latent carcinoma, the types of treatment available, and the probable errors of biopsy based on variable standards of comparison which he elects to employ. If the limitations are well understood, prostatic biopsy can be of definite help to the urologist in the clinical management of patients with prostatic carcinoma. On the other hand, it provides no magic key to unlock the diagnostic and therapeutic problems encountered in this serious disease.

The importance of preliminary biopsy before radical prostatectomy has been mentioned. Preliminary biopsy is equally important before a middle-aged man is sentenced to a life of estrogenic treatment or to castration. Opposition is growing in the profession to bilateral orchiectomy without preliminary confirmation of the diagnosis with either 1) positive result of tissue biopsy, or 2) evidence of metastasis.

The growing incidence of non-tuberculous granulomatous prostatitis is an increasingly important and disturbing factor in differential diagnosis. As Thompson and Albers pointed out in 1953, the findings on digital-rectal and cystoscopic examinations and the symptoms may be identical to those of carcinoma of the prostate, so that diagnosis can be made only by biopsy. In Culp's Mayo Clinic series of 107 biopsies at open perineal operations, 12 of the 24 which did *not* show carcinoma did exhibit granulomatous prostatitis.

PART II. ANALYSIS OF 203 CASES OF TRANSRECTAL BIOPSY: WITH COMMENT AND SUMMARY OF PARTS I AND II

Material for study. We began to use transrectal biopsy of the prostate at the Mayo Clinic in November 1956, and from that time until May 1, 1961, it has been performed in 203 patients; 198 of these were 50 years or older; the other five were between 40 and 50 years of age. In 3 cases satisfactory tissue for examination was not obtained; this report, therefore, will deal with 200 cases in which tissue was adequate for satisfactory microscopic examination. All specimens were removed by consultants in the Section of Proctology, on request of the consultants in the Section of Urology.

Technique. All biopsies were performed in the hospital, each patient being hospitalized for 18 to 24 hours. Enemas were given until the water returned clear, and a size 18F Foley urethral catheter was inserted and left indwelling overnight. A sulfonamide was given orally the day of, and daily for a week following, the procedure. Caudal block anesthesia was used in most cases, although caudal and trans-sacral block was needed to secure sufficient anal relaxation in some cases, and pentothal sodium anesthesia was used in a few.

A Fansler operating type of anoscope was introduced carefully through the anus to avoid making anal skin abrasions. The lower part of the rectum including the mucosa overlying the prostate was painted with a suitable antiseptic. The prostate was palpated with an index finger inserted through the anoscope to determine the proper site for insertion of the needle. The Silverman needle then was introduced with the index finger of the right hand (fig. 1, *A*). After the proctologist had selected the site for biopsy, using the left hand he pushed the needle through the rectal mucosa, Denonvilliers' fascia, and just into the prostatic capsule. Usually the needle was directed outward and upward, since questionable areas are most frequently in the periphery of the gland. The bevel of the needle was turned medially to avoid injuring the urethra. With the needle stationary, the proctologist withdrew the stylet, inserted the inner or split needle and advanced it into the suspected prostatic tissue for about 1 to 1.5 cm. (fig. $1B_1$) and engaged a section or core of tissue. The outer cannula then was advanced over the prongs of the split needle, thus trapping a core of tissue (fig. $1B_2$). The entire instrument was rotated slightly to loosen the core, following which the needle was withdrawn. We have repeated this procedure as many as four times or until adequate tissue for examination was obtained. It is usually wise to biopsy both lobes of the gland even though only one side feels neoplastic, because not infrequently the lobe that feels benign will furnish the "positive" tissue. In 3 cases in-

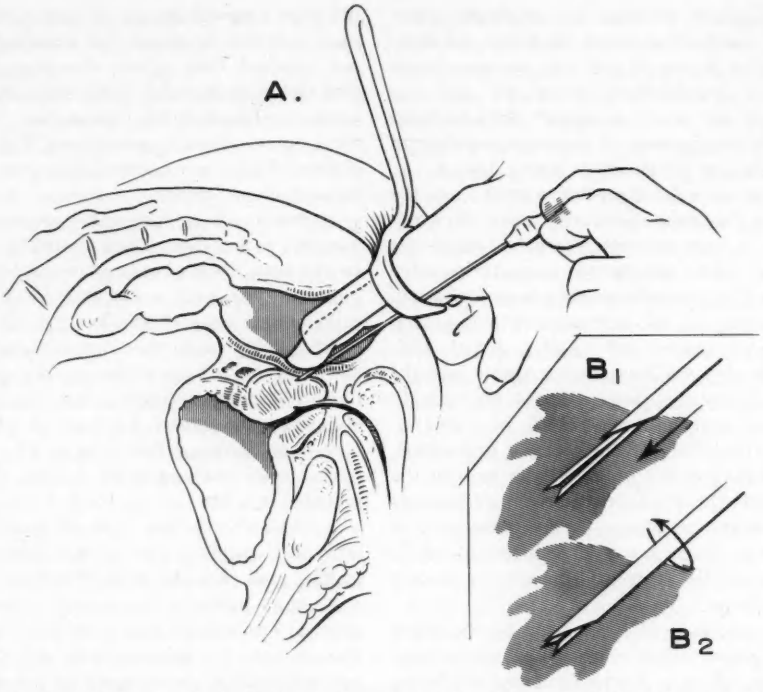


FIG. 1. *A*, tip of Silverman needle is thrust through rectal wall into gland. B_1, advancement of split needle into glandular tissue. B_2, outer cannula advanced over prongs of split needle, trapping core of tissue.

adequate tissue was obtained with the Silverman needle; therefore, an incision was made in the rectal mucosa, and tissue was obtained with biopsy forceps.

In an occasional case fresh frozen sections were examined after staining with polychrome methylene blue. In most cases, however, the pathologists preferred to examine 24-hour fixed paraffin sections because of the small size of the pieces of tissue.

Selection and classification of cases for biopsy. Cases selected for biopsy have fallen into three groups. Group 1 included the cases in which digital-rectal examination revealed a firm palpable nodule or localized area of induration in the prostate, and radical prostatectomy was not being considered as a possible method of treatment. There was no evidence of metastasis in this group. Group 2 is comprised of cases in which more or less diffuse induration involved an entire lobe or the entire prostate. In these cases the urologist could not be sure if he was dealing with just "firm" benign hyperplasia, prostatitis, or carcinoma, and insufficient urinary obstruction existed to warrant transurethral resection or open prostatectomy. There was no evidence of metastasis in this group. Group 3 included the cases in which metastasis was demonstrated clinically or on roentgenologic examination. The reader may wonder why biopsy was necessary if metastasis was present. Obviously, it is not if the prostate feels definitely malignant on palpation and *characteristic osteoplastic* metastatic lesions can be demonstrated roentgenographically, but the situation is not always that simple and clear cut. Examples of situations in which biopsy was used in this group included the following: 1) unusual types of metastasis to brain, lungs, and supraclavicular lymph nodes in which the prostate was equivocal on palpation; 2) osteolytic or mixed types of bony metastasis; 3) typical osteoplastic metastasis, yet the prostate felt either benign or normal to palpation and 4) a suspicion of malig-

nancy on palpation, but biopsy was performed before results of the x-ray studies were reported. Either this was an error or metastasis was not suspected.

It will be immediately evident to the experienced urologist that groups 1 and 2 are not easily separable or distinct entities. It is often difficult to decide whether a firm area is a distinct nodule or whether the entire lobe is firm. Varied opinions may be expressed by experienced urologists after examining the same patient. In this study we have used the urologist's opinion of the digital-rectal examination as written on the patient's record. Whenever he seemed to question whether the lesion represented a nodule or a more diffuse involvement, the case has been arbitrarily placed in group 2.

Group 2, therefore, includes all suspicious-feeling prostates which were not regarded as discrete nodules. For the purpose of brevity in this paper, we shall employ the term "hard prostate" (suggested by Grabstald) to describe these cases.

Of the 200 cases reported in this study, 52 belong in group 1, 115 in group 2, and 33 in group 3. From the urologist's note on the record, we have tried to ascertain whether he leaned toward or favored a diagnosis of carcinoma or benign lesion. Such statements as "probably benign but can't exclude carcinoma," "probably malignant but can't be sure," "carcinoma, 75 per cent," or "prostate equivocal" have provided us with data for this evaluation. From these opinions written by the eight urologic consultants, three diagnoses were found: 1) diagnosis of carcinoma favored, 2) diagnosis of benign lesion favored, and 3) equivocal. These opinions have been correlated with the results of biopsy.

Results of biopsy. For the purpose of brevity, we shall use the terms "positive" and "negative" biopsies; "positive" indicating that carcinoma was found; "negative" that it was not found. The results of biopsy are shown in table 3. Of the entire group of 200 cases in which biopsy was satisfactory, 118 (59 per cent) were positive. Positive biopsies were obtained in 50 per cent of the group 1 cases, in 56 per cent of the group 2 cases and in 85 per cent of the group 3 cases (demonstrable metastasis). A word of explanation is in order concerning the 33 cases in group 3. In 28 of these cases osseous metastasis was demonstrated by roentgenologic examination.

TABLE 3. *Results of 200 satisfactory transrectal biopsies of the prostate*

Clinical classification based on digital-rectal examination of prostate	Total cases	No carcinoma found	Carcinoma present	
			Cases	Per cent
Group 1 Palpable nodules—no metastasis demonstrable	52	26	26	50
Group 2 Hard prostate—no metastasis demonstrable	115	51	64	56
Group 3 Prostate variable on digital-rectal palpation—metastasis	33	5	28	85
Total cases	200	82	118	59

In three of these 28 cases, non-osseous metastasis also was demonstrated clinically: in 2 cases to the lung and in one to the supraclavicular nodes (proved by biopsy). In the remaining 5 cases bony metastasis was not apparent on roentgenologic examination, but clinical evidence of metastasis was present in the brain in 2 cases, in the lungs in two and in the bone marrow in one. The prostate was considered to be malignant clinically in four of the 5 cases in which transrectal biopsy was negative. In the fifth case, metastasis had occurred to the lung; in this case the result of biopsy was considered correct and the primary lesion was considered *not* to be in the prostate.

Correlation of biopsy with digital-rectal examination in groups 1 and 2: In table 4 we have correlated the results of transrectal biopsy with the diagnosis which the urologic consultant favored or leaned toward from his digital-rectal examination. In this comparison we have used only groups 1 and 2 because we felt that the presence of metastasis tended to influence the opinion. When the diagnosis of carcinoma was favored on this basis, it was substantiated by biopsy in 63 per cent of cases; when a diagnosis of a benign lesion was favored, it was substantiated in only 54 per cent of cases; whereas when the urologist did not commit himself as favoring one or the other diagnosis, carcinoma was found in 39 per cent of the biopsies. This lack of cor-

relation between findings on digital-rectal examination and biopsy reflects the relative unreliability of the digital-rectal examination, especially in questionable cases, and lends support to Hudson's contention that there is little or no correlation between findings on digital-rectal examination and on histologic examination of the prostate.

Grade of carcinoma: The microscopic grading (Broders' classification) of the positive biopsies correlated with the clinical grouping is shown in table 5. About the only point of interest here is that 3 cases in the metastatic group (approximately 10 per cent) were only grade 1. This is somewhat reminiscent of results of a previous study by one of us (J.L.E.) and others in which approximately 10 per cent of the grade 1 lesions of the prostate had metastasized.

TABLE 4. *Correlation of results of transrectal biopsy in 167 cases without metastasis (groups 1 and 2) with diagnosis favored by urologist*

Urologic opinion based on digital-rectal examination	Transrectal biopsy		
	Total cases	Carcinoma present	
		Cases	Per cent
Carcinoma favored	95	60	63
Benign disease favored	26	12	46
Equivocal: Neither diagnosis favored	46	18	39
Total cases	167	90	54

TABLE 5. *Correlation of microscopic grading* of carcinoma found on transrectal biopsy with clinical grouping*

Clinical grouping	Total cases	Carcinoma, grade*			
		1	2	3	4
No metastasis					
Group 1	26	3	19	4	0
Group 2	64	13	36	14	1
Metastasis					
Group 3	28	3	15	9	1
Total	118	19	70	27	2

* Broders' classification, grades 1 to 4.

TABLE 6. *Pathologic diagnosis in 82 cases in which carcinoma was not found on biopsy*

Classification	Total cases	Pathologic diagnosis, cases			
		Benign prostatic hypertrophy	Normal prostate	Granulomatous prostatitis	Chronic prostatitis
Group 1	26	18	5	1	2
Group 2	51	34	11	1	5
Group 3	5	5			
Total	82	57	16	2	7

Pathologic diagnosis when biopsies were negative: The pathologic diagnosis in the 82 cases in which biopsy did not show carcinoma is shown in table 6. The most frequent finding was benign prostatic hyperplasia, with normal prostatic tissue coming next. Chronic prostatitis was found in 7 cases and granulomatous prostatitis in two. The surprising finding here is that granulomatous prostatitis was present in only 2 cases, an incidence of approximately 1 per cent of the 200, whereas in the 107 cases of open perineal biopsy at the clinic reported by Culp in 1959 there were 12, an incidence of approximately 11 per cent.

Accuracy of transrectal biopsy. The serious error which occurs in biopsy is, of course, reporting benign tissue when carcinoma is present. As pointed out in the first part of this paper, the only method to determine absolutely the accuracy of biopsy would be removal and examination of the entire prostate by means of the step-section method. Transrectal biopsy is rarely done, however, when prostatectomy is being considered for relief of urinary obstruction, because a better histologic examination can be performed after the prostate has been removed. Other less reliable methods of determining accuracy are comparisons with 1) clinical data, 2) other forms of biopsy including open perineal biopsy, and 3) examination of random sections of prostatic tissue removed either by transurethral resection or open prostatectomy. The meager data available in this study for such comparisons are as follows:

In four of 33 (12.1 per cent) patients with metastasis (group 3) biopsy revealed benign tissue, yet clinically the prostate was malignant without question.

In one (1.9 per cent) of 52 cases in group 1 the biopsy revealed only benign tissue, but the prostate was considered clinically malignant.

In five (4.3 per cent) of 115 cases, biopsy revealed benign tissue, but the prostate was considered malignant on the basis of positive tissue found 1) at transurethral resection in 3 cases, 2) at necropsy* in 1 case, and 3) clinically in 1 case. This makes a total of known false negative biopsies in 10 of the total 200 cases (5.0 per cent). It is obvious that if open perineal biopsy or histologic examination of each prostate (removed surgically or at necropsy) could have been carried out, the percentage of error would no doubt have been greater. Just how much greater is only conjecture, and of course would depend on the standard used for comparison: open perineal biopsy would suggest the least error, random sections of the removed prostate the next, and step sections of the removed prostate the highest percentage of error. In no case was a positive biopsy challenged or proved false.

Other miscellaneous data of interest in this evaluation of accuracy include the following. In 1 case, transrectal biopsy revealed benign tissue. This diagnosis was subsequently proved at open perineal biopsy. In 3 patients, only one lobe was considered firm clinically, but the positive tissue was found only in the opposite lobe. In 8 patients one lobe only was considered firm clinically, yet positive tissue was obtained from both lobes.

Treatment. The treatment instituted in the 90 cases in groups 1 and 2 (no metastasis) in which biopsy showed carcinoma and in the 32 cases with metastasis in group 3 in which carcinoma was considered to be present, is summarized in table 7.

If the 5 patients treated by radical prostatectomy are excluded, only 6 patients in groups 1 and 2 were sent home without some type of endocrine treatment (estrogens, orchiectomy or both). All patients in group 3 were given endocrine therapy. We have been cautiously exploring the use of external radiation with radioactive cobalt in a few selected cases. We advised it as the only treatment in 2 cases in this series and in conjunction with orchiectomy in four other cases. When orchiectomy was done, estrogens were administered also in most cases.

* This was the only death in this series. See Complications.

TABLE 7. *Treatment in the 118 cases of carcinoma proved by biopsy plus 4 cases of carcinoma proved by demonstration of metastasis*

Type of treatment	Clinical grouping		
	No metastasis		Metastasis, group 3
	Group 1	Group 2	
No treatment advised	1	3	0
Estrogens only	16*	37†‡	10†
Orchiectomy only	0	4§	0
Orchiectomy and estrogens	4‡	17	22‡
Orchiectomy advised, done elsewhere	0	1	0
Radical perineal prostatectomy (at clinic)	4	0	0
Radical perineal prostatectomy (elsewhere)	1	0	0
External irradiation (Co^{60}) only	0	2	0
Total cases (122)	26	64	32

* Orchiectomy advised but refused in 1 case.
† Orchiectomy advised but refused in 3 cases.
‡ Transurethral resection also in 1 case.
§ Co^{60} irradiation also administered in 1 case.

The five radical prostatectomies were performed early in our experience. As stated previously, we now avoid transrectal biopsy if radical perineal prostatectomy is considered because the procedure tends to increase the difficulty of the surgical dissection. In such cases open perineal biopsy with immediate operation if the biopsy is positive is the procedure of choice.

In table 8, the type of endocrine therapy advised is correlated with the three clinical groups. Our use of orchiectomy in patients without evidence of metastasis is increasing. This trend no doubt has been influenced by the results of our recent 10-year survival analysis of endocrine therapy in 1101 patients with carcinoma of the prostate by one of us (J.L.E.) and Greene and Papantoniou.

Complications. Aside from one unexpected and unexplainable death early in our experience (the thirty-sixth case in the series), complications have been minimal and relatively unimportant. Slight gross hematuria was mentioned in the records of 5 patients. Most patients, however, were dismissed from the hospital the day following biopsy. Closer follow-up might

TABLE 8. *Endocrine treatment advised in 111 of the 122 cases of carcinoma proved by biopsy or by demonstration of metastasis*

	Total cases	Orchiectomy alone or with estrogens advised*		Estrogens only advised	
		Cases	Per cent	Cases	Per cent
No metastasis					
Group 1.....	26	5	19	15	58
Group 2.....	64	25	39	34	53
Metastasis					
Group 3.....	32	25	78	7	22

* When orchiectomy was advised but refused (see footnotes to table 7), the cases are listed in this table under the heading orchiectomy alone or with estrogens advised. In table 7, these cases are listed under the actual treatment given.

have revealed this complication to be a little more frequent. Transient pyuria or dysuria with or without fever also has been observed occasionally. This responded quickly to sulfonamide therapy. Although we have not sent out letters of inquiry to these patients, a review of correspondence in their records has uncovered no evidence of delayed complications after leaving the clinic.

The one death in the series occurred in 1957 on the sixth post-biopsy day in a 60-year-old normotensive man with proved carcinoma. The transrectal biopsy procedure, done under caudal and trans-sacral anesthesia, appeared to be entirely uneventful. On the third day following biopsy anuria of obscure origin developed; cystoscopy and catheterization of the ureters revealed no evidence of gross urinary obstruction. The anuria persisted and the azotemia increased in severity despite all forms of treatment. Immediately prior to his death the patient complained of severe pain in the left side of the thorax. Necropsy revealed recent large myocardial infarction, acute tubular nephrosis, and carcinoma of the prostate. The possibility of sensitivity to anesthetic agents or medication as a contributing cause of death was considered.

COMMENT ON PARTS I AND II

Diagnosis and treatment of carcinoma of the prostate is not a simple problem of periodic digital-rectal examinations in men more than 50 years of age to detect early nodules that are suspected of being malignant and apply appropriate treatment. The preponderance of evidence suggests that the palpable nodule is not an early manifestation of the disease. The incidence of carcinoma of the prostate in men 50 years of age or older depends on the thoroughness and completeness of the histologic examination; thus, by open perineal biopsy it is approximately 11 per cent; by routine examination of the removed prostate (either at surgery or necropsy) with examination of only random sections, it is approximately 13 per cent; whereas, if the step-section method of examination is used, it is approximately 24 per cent.

Malignant lesions of the prostate which can be detected clinically by one, or a combination of, digital-rectal examination, obstructive symptoms or demonstration of metastatic lesions have been called "manifest" cancer. Those that cannot be detected in this manner are spoken of rather loosely as "latent" or "occult" carcinoma. No histologic evidence has yet been presented to indicate that there is any basic difference between latent and manifest carcinoma. The natural history of carcinoma of the prostate is not known, but evidence suggests it may require as long as 20 years for a latent lesion to become manifest.

The diagnostic length to which a physician will go to detect early cancer of the prostate is probably proportionate to his convictions concerning the efficacy of the various available methods of treatment. For instance, is he concerned about latent or occult cancer, or is he satisfied to deal only with manifest cancer, that is, palpable nodules, and diffuse induration? Is he an advocate of radical prostatectomy for carcinomatous nodules, or does he prefer endocrine management or no treatment until symptoms of obstruction or metastasis, or both, appear? In cases in which diffuse carcinomatous involvement of either one or both lobes of the prostate is present, does he favor early, late, or no endocrine management?

Good judgment seems to demand that, regardless of convictions concerning treatment, diagnosis should always be as accurate and meticulous as is consistent with good clinical judgment. It is disquieting to the urologist, the referring physician, and the patient himself if

the final diagnosis is "prostate of questionable consistency; impossible to say if carcinoma is present or not; observe, re-examine in 6 months." As a method of reducing the number of such indeterminate diagnoses, we have been pleased with transrectal biopsy. It is a simple procedure, both for the patient and physician, and can be employed as freely as most more-or-less routine diagnostic procedures. Our patients have neither objected to, nor complained about, the procedure. Although we are aware of the limitations of transrectal biopsy, we also realize that few diagnostic procedures in medicine are infallible. It has greatly improved the quality of our diagnosis by reducing the number of patients whom we dismiss from the clinic with an indeterminate diagnosis as far as the prostate is concerned. The acceptance of this diagnostic procedure by the urologic consultants is demonstrated by the steadily increasing number of patients who are referred for this procedure each year, as follows: last 2 months of 1956, two patients; 1957, 39; 1958, 27; 1959, 31; 1960, 68, and in the first 4 months of 1961, 36.

SUMMARY

Opinions expressed in the literature concerning the incidence, site of origin, natural history of prostatic carcinoma, and relative value of various types of prostatic biopsy have been reviewed.

An analysis has been made of 203 patients subjected to transrectal biopsy of the prostate at the Mayo Clinic from November 1956, to May 1, 1961. In 200 cases the specimen was considered adequate for examination. In 118 (59 per cent) of the 200 cases, biopsy revealed carcinoma. The 200 cases were divided into 3 groups: In the 52 cases in group 1, nodules were palpable and there was no metastasis; in the 115 cases in group 2, diffuse induration of one or both lobes was present without metastasis, and in the 33 cases in group 3 metastasis was present. Biopsy revealed carcinoma in 50 per cent, 56 per cent and 85 per cent of the cases in these respective groups. In groups 1 and 2 correlation was poor between the diagnosis favored by the urologist from his digital-rectal examination and that reported from biopsy. The problems of accuracy of biopsy and false-negative reports have been discussed. Biopsy of both lobes of the prostate is important because not infrequently the carcinomatous tissue is obtained from the lobe which does not feel malignant, or from both lobes when only one is suspected. Endocrine treatment of some type (either orchiectomy or estrogens or both) was advised in 91 per cent of the 122 cases in which carcinoma was found to be present (88 per cent of the cases in which no metastasis was present and in 100 per cent of cases in which metastasis was present). Orchiectomy was advised in approximately a third of the patients without metastasis (groups 1 and 2) and in approximately four-fifths of the patients with metastasis (group 3).

REFERENCES

ADRION, WALTER: Ein Beitrag zur Ätiologie der Prostatahypertrophie. Beitr. path. Anat., **70:** 179–202, 1922.

ALBARRAN, J. AND HALLÉ, N.: Hypertrophie et néoplasies épithéliales de la prostate. Ann. maladies organes genito-urinaires, **18:** 113–147, 1900.

ALBARRAN, J. AND MOTZ, B.: Contribution à l'étude de l'anatomie macroscopique de la prostate hypertrophiée. Ann. maladies organes genito-urinaires, **20:** 769–817, 1902.

ALLEMANN, R.: Prostatahypertrophie und Prostatakrebs: Ein Beitrag zur Frage du okkulten Karzinome. Schweiz. med. Wchnschr., **82:** 147–154, 1952.

ANDREWS, G. S.: Latent carcinoma of the prostate. J. Clin. Path., **2:** 197–208, 1949.

ASTRALDI, ALEJANDRO: Diagnosis of cancer of the prostate: Biopsy by rectal route. Urol. & Cutan. Rev., **41:** 421–427, 1937.

BAKER, ROGER: Studies on cancer prevention in urology. Ann. Surg., **137:** 29–35, 1953.

BARNES, R. W. AND EMERY, D. S.: Management of early prostatic carcinoma. Calif. Med., **91:** 57–61, 1959.

BARON, E. AND ANGRIST, A.: Incidence of occult adenocarcinoma of the prostate: After 50 years of age. Arch. Path., **32:** 787–793, 1941.

BERGMAN, R. T., TURNER, R., BARNES, R. W. AND HADLEY, H. L.: Comparative analysis of one thousand consecutive cases of transurethral prostatic resection. J. Urol., **74:** 533–545, 1955.

BIANCHI, FRANCO: Practical advantages of the perineal biopsy of the prostate. J. Urol., **76:** 645–650, 1956.

BIBUS, B.: Die Beziehungen zwischen Adenom und Carcinom der Prostata und ihre Bedentung für die Behandlung. Ztschr. urol. Chir., **43:** 357–361, 1937.

CLARKE, B. G., LEADBETTER, W. F. AND CAMPBELL, J. S.: Implantation of cancer of the prostate in site of perineal needle biopsy: Report of a case. J. Urol., **70:** 937–939, 1953.

COLBY, F. H.: Carcinoma of the prostate: Results of total prostatectomy. J. Urol., **69:** 797–806, 1953.

CULP, O. S.: Significance and treatment of prostatic nodules. J. Mich. Med. Soc., **58:** 585–594, 1959.

CULP, O. S. AND MCDONALD, J. R.: Importance of frozen sections in evaluating prostatic nodules. J. Urol., **72:** 443–449, 1954.

DAVES, J. A., TOMSKEY, G. C. AND COHEN, A. E.: Transrectal needle biopsy of the prostate. J. Urol., **85:** 180–182, 1961.

DOSSOT, RAYMOND: Cancer of the prostate: Its origin and extension. J. Urol., **23:** 217–245, 1930.

EDWARDS, C. N., STEINTHORSSON, E. AND NICHOLSON, D.: An autopsy study of latent prostatic cancer. Cancer, **6:** 531–554, 1953.

EMANUEL, M. AND FOOTE, E. L.: Transrectal needle biopsy in the diagnosis of prostatic carcinoma. J. Maine M. A., **48:** 234–238, 1957.

EMMETT, J. L., GREENE, L. F. AND PAPANTONIOU, A.: Endocrine therapy in carcinoma of the prostate gland: 10-Year survival studies. J. Urol., **83:** 471–484, 1960.

FERGUSON, R. S.: Recent advances in the diagnosis of carcinoma of the prostate. Canad. M. A. J., **29:** 497–501, 1933.

FINKLE, A. L.: Genito-urinary tract infection, prostatic calculi and carcinoma of the prostate. J. Urol., **71:** 67–81, 1954.

FLOCKS, R. H.: Newer developments in the management of early prostatic cancer. Postgrad. Med., **28:** 46–50, 1960.

FRANKS, L. M.: Benign nodular hyperplasia of the prostate: A review. Ann. Roy. Coll. Surg. England, **14:** 92–106, 1954. (A)

FRANKS, L. M.: Latent carcinoma of the prostate. J. Path. & Bact., **68:** 603–616, 1954. (B)

GAYNOR, E. P.: Zur Frage des Prostatakrebses. Arch. path. Anat., **301:** 602–652, 1938.

GERAGHTY, J. T.: Treatment of malignant disease of the prostate and bladder. J. Urol., **7:** 33–65, 1922.

GIL VERNET, S.: Patología urogenital. Tomo 1, Cancer de Prostata. Barcelona: Editorial Miguel Servet, 1944, p. 17.

GLOGGENGIESSER, W.: Untersuchungen über das sogenannte latente Prostatacarcinom. Frankfurt. Ztschr. Path., **69:** 279–301, 1958.

GOLDMAN, E. J. AND SAMELLAS, W.: Local extension of carcinoma of the prostate following needle biopsy. J. Urol., **84:** 575–576, 1960.

GRABSTALD, H.: Further experience with transrectal biopsy of the prostate. J. Urol., **74:** 211–221, 1954.

GRABSTALD, H.: Summary of currently employed prostatic biopsy methods, with comments concerning combined transrectal biopsy and radical retropubic prostatectomy. Brit. J. Urol., **28:** 176–186, 1956.

GRABSTALD, H.: The hard prostate. Texas J. Med., **53:** 703–705, 1957.

GRABSTALD, H. AND ELLIOTT, J. L.: Transrectal biopsy of the prostate. J.A.M.A., **153:** 563–565, 1953.

GRAHAM, W. H.: Carcinoma of the prostate. Brit. J. Urol., **30:** 389–391, 1958.

GREENE, L. F. AND SIMON, H. B.: Occult carcinoma of the prostate: Clinical and therapeutic study of eighty-three cases. J.A.M.A., **158:** 1494–1498, 1955.

HARRISON, J. H. AND POUTASSE, E. F.: The choice of operative approach for prostatectomy. J. Urol., **63:** 132–146, 1960.

HIGBEE, D. R.: Perineal surgery in carcinoma of prostate. J. Urol., **69:** 144–151, 1953.

HINMAN, F., JR.: The early diagnosis and radical treatment of prostatic carcinoma. Calif. Med., **68:** 338–343, 1948.

HINMAN, F., JR.: Open vs. needle biopsy in early diagnosis of prostatic cancer. AMA Arch. Surg., **70:** 475, 1955.

HIRST, A. E., JR. AND BERGMAN, R. T.: Carcinoma of the prostate in men 80 or more years old. Cancer, **7:** 136–141, 1954.

HOLTGREWE, L. AND VALK, W. L.: Factors influencing mortality and morbidity of transurethral prostatectomy. Trans. Am. Assn. Genito-Urin. Surg., **53:** 75–84, 1961.

HORSTMANN, W.: Pathologisch-anatomische Untersuchungen über Geschwulstartige Erkrankungen der Prostata, insbesondere über das Karzinom. Ztschr. Urol., **45:** 50–59, 1952.

HUDSON, P. B.: Prostatic cancer: Its incidence, extent and behavior in 686 men studied by prostatic biopsy. Am. Geriatrics Soc., **5:** 338–350, 1957.

HUDSON, P. B., FINKLE, A. L., JOST, H. M., TRIFILIO, A. AND STOUT, A. P.: Prostatic cancer: Comparison of open and "punch" biopsy techniques. AMA Arch. Surg., **70:** 508–512, 1955.

HUDSON, P. B., FINKLE, A. L., TRIFILIO, A., JOST, H. M., SPROUL, E. E. AND STOUT, A. P.: Prostatic cancer. VIII. Detection of unsuspected adenocarcinoma in the aging male population. J.A.M.A., **155:** 426–429, 1954. (A)

HUDSON, P. B., FINKLE, A. L., TRIFILIO, A. AND WOLAN, C. T.: Prostatic cancer: Value of transurethral biopsy in search of early prostatic carcinoma. Surgery, **35:** 897–900, 1954. (B)

HUGGINS, C. AND WEBSTER, W. O.: Duality of human prostate in response to estrogen. J. Urol., **59:** 258–266, 1948.

HUNT, V. C.: Surgery of the prostate. J. Iowa M. Soc., **14:** 171–174, 1924.

HUNT, V. C.: Modern methods of treating prostatic obstruction. J. Mich. M. Soc., **29:** 116–120, 1930.

JACOBY, MAX: Zur Prostatahypertrophie. Ztschr. urol. Chir., **14:** 6–37, 1923.

JEWETT, H. J.: Radical perineal prostatectomy for carcinoma: An analysis of cases at Johns Hopkins Hospital, 1904–1954. J.A.M.A., **156:** 1039–1041, 1954.

JEWETT, H. J.: Radical perineal prostatectomy for early cancer. Bull. New York Acad. Med., **34:** 26–33, 1958.

JOHNSON, F. P.: The later development of the urethra in the male. J. Urol., **4:** 447–502, 1920.

JORES, LEONH: Ueber die Hypertrophie des sogenannten mittleren Lappens der Prostata. Arch. path. Anat., **135:** 224–247, 1894.

KAHLER, J. E.: Carcinoma of the prostate gland: A pathologic study. J. Urol., **41:** 557–574, 1939.

KAUFMAN, J. J., ROSENTHAL, M. AND GOODWIN, W. E.: Methods of diagnosis of carcinoma of the prostate: A comparison of clinical impression, prostatic smear, needle biopsy, open perineal biopsy, and transurethral biopsy. J. Urol., **72:** 450–465, 1956.

LABESS, MORRIS: Occult carcinoma in clinically benign hypertrophy of the prostate: A pathologic and clinical study. J. Urol., **68:** 893–896, 1952.

LE DUC, I. E.: Anatomy of prostate and pathology of early benign hypertrophy. J. Urol., **42:** 1217–1241, 1939.

LOWSLEY, O. S.: The development of the human

prostate gland with reference to the development of other structures at the neck of the urinary bladder. Am. J. Anat., **13:** 299–349, 1912.

LUPPI, J. E.: Investigación sobre el cáncer oculto de la próstata. Rev. méd. Rosario, **37:** 845–861, 1947.

MEMMELAAR, JOSEPH: Total prostatovesiculectomy—Retropubic approach. J. Urol., **62:** 340–348, 1949.

MEYENBURG, H. AND CATHOMAS, B.: Ueber die Häufigkeit des Prostata-Karzinoms in Zürich. Schweiz. med. Wchnschr., **78:** 473–475, 1948.

MOORE, R. A.: The morphology of small prostatic carcinoma. J. Urol., **33:** 224–234, 1935.

MOTZ, B. AND PEREARNAU: Contribution à l'étude de l'évolution de l'hypertrophie de la prostate. Ann. maladies organes genito-urinaires, **23:** 1521–1548, 1905.

MUIR, E. G.: Carcinoma of the prostate. Lancet, **1:** 667–672, 1934.

MYERS, G. M.: The occurrence of carcinoma in clinically benign prostatic obstructions. Colorado Med., **34:** 248–251, 1937.

NEEDELL, M. H., SLOTKIN, G. E., MITCHELL, F. D. AND FRIEDMANN, M.: Prostatic needle biopsy. J. Urol., **74:** 138–141, 1955.

OSWALD, WALTER: Häufigkeit und Genese des Prostatacarcinoms. Frankfurt. Ztschr. Path., **55:** 296–316, 1941.

PALOMO, ALEJANDRO: Carcinoma of the prostate gland. J. Urol., **53:** 166–187, 1945.

PEARLMAN, C. K.: Transrectal biopsy of prostate. J. Urol., **74:** 387–392, 1955.

PECK, SAM: Needle biopsy of prostate. J. Urol., **83:** 176–180, 1960.

PEIRSON, E. L. AND NICKERSON, D. A.: Biopsy of the prostate with the Silverman needle. New Eng. J. Med., **228:** 675–678, 1943.

RICH, A. R.: On the frequency of occurrence of occult carcinoma of the prostate. J. Urol., **33:** 215–223, 1935.

RINKER, J. R. AND SHUMAN, W. G.: Perineal punch biopsy of prostate: with statistical analysis. J. Urol., **67:** 709–712, 1952.

SHAW, E. C.: An early case of carcinoma of the prostate associated with benign hypertrophy. J. Urol., **11:** 63–73, 1924.

SMITH, G. G. AND WOODRUFF, L. M.: The development of cancer of the prostate after subtotal prostatectomy. J. Urol., **63:** 1077–1080, 1950.

SPRING, W. B. AND ALDEN, M. W.: An evaluation of the needle biopsy in the diagnosis of prostatic carcinoma. Canad. M. A. J., **70:** 179–185, 1954.

SWAN, R. H. J.: The incidence of malignant disease in the apparently benign enlargement of the prostate. Lancet, **2:** 971–974, 1923.

SWYER, G. I. M.: Post-natal growth changes in the human prostate. J. Anat., **78:** 130–145, 1944.

THOMPSON, G. J. AND ALBERS, D. D.: Granulomatous prostatitis: A condition which clinically may be confused with carcinoma of prostate. J. Urol., **69:** 530–538, 1953.

TREIGER, P., WELFELD, J. AND MARX, J.: Suprapubic prostatectomy: A review of 108 cases. Urol. & Cutan. Rev., **52:** 8–9, 1948.

VEENEMA, R. J.: A simplified prostatic perineal biopsy punch. J. Urol., **69:** 320–322, 1953.

WADE, H.: Prostatism: The surgical anatomy and pathology of operative treatment. Ann. Surg., **59:** 321–359, 1914.

WALTHARD, B.: Die Häufigkeit und Histogenese des Prostatacarcinoms. Ztschr. urol. Chir., **43:** 483–496, 1937.

WEBB, E. A. AND SMITH, B. A., JR.: Radical perineal prostatectomy. J. Urol., **75:** 1000–1005, 1956.

WHITMORE, W. F., JR.: Hormone therapy in prostatic cancer. Am. J. Med., **21:** 697–713, 1956.

WILSON, L. B. AND MCGRATH, B. F.: Surgical pathology of the prostate: A review of 468 cases. Surg., Gynec. & Obst., **13:** 647–681, 1911.

YOUNG, H. H.: The ultimate results in the treatment of carcinoma of the prostate by the radical removal of the prostate, vesical neck and seminal vesicles. J. Urol., **29:** 531–543, 1933.

YOUNG, H. H.: Tumors of the prostate. In: Lewis' Practice of Surgery. Hagerstown, Md.: W. F. Prior Company, Inc., 1955, vol. 9, chapt. 21, p. 27.

DISCUSSION

DR. JOHN A. TAYLOR (New York, N. Y.): I just want to say that I was very much interested in Dr. Chute's paper. It is an entirely new concept of stone formation. Stone formation always brings up the question of dissolution. I wondered if he thinks he might have helped some of these cases along with some of our agents. We have been interested in stone dissolution for years using Suby's solution. In fact, those of you who were in Athens at the meeting of the International Society of Urology remember that I presented a series of cases of stones dissolved in the kidney. They were for the most part fragments that were left behind. They were small calculi.

Naturally, when renacidin came along, we were very much interested in trying it. While it hasn't all been moonlight and roses, I would just like to show you one of the most startling things I have seen in my practice.

(Slide) Here is a woman. You can notice a staghorn calculus completely filling her kidney.

(Slide) There it is five days after a constant drip with renacidin.

QUESTION: What per cent?

DR. TAYLOR: I can't tell you. Just follow the directions on the bottle. (Laughter) We have a druggist who makes it up for us in our hospital.

We have found that the best way to drip solution into a kidney is with a small single catheter. That is a size 4 catheter. Hit it high, drip the solution in and let it come around the catheter. If you put two catheters in, the return gets plugged all the time, and you have chills and fever.

(Slide) That's 10 days. The stone is gone. That was done in October. I saw the patient just before I left. She has a 3-minute P.S.P. output from the left kidney, and no infection. Her pyelogram looks good.

DR. JOHN K. ORMOND (Pontiac, Mich.): I wanted to report two experiences with renacidin. One was my own, and one was of a friend of mine. There was a patient with nephrostomy drainage and a large calculus in the kidney pelvis. Renacidin was used; it destroyed the kidney, and caused the death of the patient.

The other was one that was very fortunate for the patient and a little bit unfortunate for me.

Following excision of a ureterocele in a 4-year-old boy, a stone developed, and I removed it. Some months later another stone developed. The only thing I could think of was to remove the stone. The patient's father decided that he wanted another opinion, so he called in Dr. Waite Bohne, my former associate, and sent the boy to the Ford Hospital. Dr. Bohne instituted renacidin irrigations and dissolved the stone. The patient was saved an operation.

DR. J. HARTWELL HARRISON (Boston, Mass.): We have had the same experience Dr. Chute has had with rupture of these catheters. I do not understand why the fingernail bit of rubber flips off, Dr. Chute; maybe you can tell us.

I would like to make one comment with regard to Dr. Valk's brilliant and very detailed presentation, the most detailed analysis I have seen of prostatic surgery. Dr. Valk commented on the fact that after 2 weeks of drainage, no matter how severely renal function was damaged, one got a measured maximum return of function. Perhaps this is true, but the benefits to be derived from this return of measured maximum function may not occur until several weeks or maybe months have passed. I am certain that he didn't mean to imply that this was not the case, but I wanted to emphasize this point. We do get added benefits from waiting until this return of renal function has had its maximum antibiotic effect on protein metabolism.

I would like to have Dr. Valk comment on the effects on renal function of the prolonged transurethral prostatectomy, those that went 90 to 120 minutes. Did you study any change in renal damage in those cases?

I may have missed your reference to infection as a complication. Perhaps you might comment on that, the incidence of urethritis and cystitis complicating prostatectomies.

I would like to ask Dr. Emmett if he had any complications at all.

DR. DAVID M. DAVIS (Haverford, Pa.): Dr. Harrison has said most of what I had in mind to say; but since I date back to the time when we had a great many more patients with extended histories and renal insufficiency, perhaps a word might be in order.

In the old days when patients had renal insufficiency, we used to drain them a long time

with suprapubic drainage. Exactly how long it should be remained somewhat mysterious. Usually one got around that by deciding to wait a little bit longer. Sometimes it went up to weeks and months.

The one thought that occurs to me is that in view of our increasing knowledge of ureteral function, perhaps in a good many of these cases the parenchyma of the kidney can scarcely return to normal until the intrapelvic pressure becomes normal; and the restoration of normal intrapelvic pressure will depend on the restoration of normal ureteral function. That may take quite a while.

One method of helping ourselves to find out about it would be to take repeated intravenous urograms and wait until the ureter presented a normal picture before thinking of going ahead with a prostatic operation.

DR. WYLAND F. LEADBETTER (Boston, Mass.): I have just a comment about transrectal biopsy of the prostate. Our experience parallels Dr. Emmett's. We began about the same time. We have done now, I would presume, somewhat over three hundred transrectal biopsies with the Silverman needle in the main.

Our experience has been as satisfactory as Dr. Emmett's, but I would like to speak a word of caution in regard to serious infectious complications, bloodstream complications. We have had at least two—and it may be three—very serious bloodstream infections following this procedure with death, I think, in 2 patients due probably to gram-negative septemia. It is possible that this may have been associated with cystoscopy, which may have been done at the same time in 2 patients.

But this is not completely an innocuous procedure. I think the patient should always be in the hospital. I am not sure but what it would be a good idea to prescribe some antibiotic. I am very much impressed with the potential seriousness of the thing. Yet I think it is one of the best diagnostic steps that we have with regard to cancer of the prostate.

I would like to ask Dr. Valk a question. He didn't have any late complications. I would be interested, if he has the figures, on how many urethral strictures occurred in that series of cases.

DR. WILLARD E. GOODWIN (Los Angeles, Cal.): I would like to comment on Dr. Emmett's paper and thank him for the data. I couldn't agree more about the value of having a definite diagnosis rather than a clinical impression. We have used transrectal biopsy a few times and have abandoned it. We continue to use perineal needle biopsies of the prostate with a Silverman needle. My associate, Dr. Joseph Kaufman, reported last month at the California Medical Association meeting on the series that he had gathered together from our services of somewhat over six hundred cases. As to accuracy of the needle biopsies, perineal needle biopsies, the figures are almost the same as Dr. Emmett has reported. We think that it gets away from the objection that Dr. Leadbetter mentioned of the danger of introducing infection from the rectum.

DR. RAYMOND G. BUNGE (Iowa City, Iowa): I would like to ask Dr. Valk what type of fluid he uses in his transurethral resection.

DR. HARRY M. SPENCE (Dallas, Texas): I would like to ask Dr. Valk how he treated the cases of extravasation.

DR. CHUTE: In answer to Dr. John Taylor, I am sure that Dr. Howard Suby would know better how to dissolve that stone. But Dr. Taylor, if I did dissolve the stone, I would be back where I was before with that piece of rubber floating up there. I think maybe that is not the thing to use in this situation. I do congratulate you on that big staghorn calculus, and I think that points a way.

In addition to the case reported by Dr. Ormond, I have heard of a case where the kidney was destroyed by the use of renacidin. Although it is very good, I think maybe you have to be careful.

May I make a couple of comments on the other papers? As regards Dr. Emmett's paper, I think I rather go along with Dr. Goodwin on sticking pretty much to the clean perineal biopsy. I think something that has made it a lot easier is this Franklin modification or the Hutchins needle, both of which are a lot longer than the old Silverman needle. They have that little shoulder built in to sort of trap the biopsy specimen. I, for one, with wise warning about septicemia, will stick to the clean perineal biopsy, going in with one of the long needles.

About Dr. Valk's paper, we tried the Burdizzo clamp. We are sold on vasectomy, and we thought that it would be wonderful to crunch, crunch, and it's all over. We liked the procedure very well for a couple of months, and then we

had two or three abscesses form inside where we made the crunch. Apparently, infection came down the vas and formed an abscess in this region. We ended by doing an orchiectomy after all. We relegated that to the museum.

I am also interested in why Dr. Valk did external urethrotomy in 23 per cent. I think it's to avoid stricture.

DR. VALK: The co-author of the paper, who did all the statistical work, would be glad to answer all these questions.

DR. H. LOGAN HOLTGREWE (Kansas City, Mo.): Thank you, Dr. Valk.

I hope I have all of the questions noted here. I didn't see some of the people. If I don't get the names correctly, you'll have to excuse me.

I'll answer Dr. Leadbetter's question first, regarding strictures. This study that we have reported on this morning is merely one phase of a rather extensive piece of work that we intend to continue in the future. Actually, as we went over the charts, I listed some eighty to ninety different items of current hospitalization. We also included in our summary the items of a long-term nature, including urethral stricture, impotence, and other complications. We are currently doing a study on this aspect of the operation.

We are encountering some inherent difficulties because of the age that we are dealing with. Many are dying of associated disorders.

I feel that we should defer any concrete answer to that, Dr. Leadbetter. It is going to be forthcoming, I hope, in the near future.

Regarding Dr. Harrison's question on cystitis and urethritis, there was a classification in the table which was called "non-specific sepsis," in which we included our cases of cystitis. In our printed paper, we will make mention of that. It was not gone into in great detail because of the problem of time.

Urethritis did not seem to be a significant complication in this series. As a matter of fact, there were no cases of phlegmon or abscess noted in the group. A mild discharge was perhaps noted; but unless some specific mention was made in the progress notes or narrative summary, in going over the chart I was helpless and couldn't record it.

Our irrigating fluid was 1.1 per cent glycine in all cases.

Our treatment of extravasation consisted of a suprapubic cystostomy with the transverse incision being employed inversely in all the cases. We placed a large cystotomy tube, a size 36 in most instances, and put large drains in the space of Retzius on other side of the bladder, always trying, of course, and effecting the drainage of the extravasated site.

We did indeed do 23 per cent urethrotomies on our patients. It is the rare instance during which we use anything but a size 28 instrument. This is particularly true, I think, of the residents who find the water flow of the larger instrument satisfactory and yielding much greater vision. It is our policy to do an external urethrotomy in any case where the size 28 is not commodiously accepted by the urethra. We hope that when we get our future work out, this will be a very important factor in reducing this rather dreaded complication of the operation.

Dr. Chute, we also find that the Burdizzo clamp is very unsatisfactory. We have also found that the incidence of vasitis, if you prefer to call it that, is extremely common. Not long ago we had a meeting of the Texas urologists in Kansas City. Dr. Valk gave our Burdizzo clamps away as door prizes. (Laughter)

DR. EMMETT: I am pleased that Dr. Leadbetter brought up this problem of inflation because it has concerned us. We have been worried about it all throughout our experience. We give patients enemas until the fluid returns clear. Then we use some antiseptic on the bowel. We have been using the sulfonamides for a day before and a week after, but I think maybe the antibiotics might be considered in view of Dr. Leadbetter's experience.

The other thing that I didn't mention is that whenever a biopsy is taken of the prostate, don't biopsy just the suspicious side or the suspicious nodule. In our experience quite often the positive biopsy comes from the opposite lobe which feels benign, or very often it comes from both lobes. This business about feeling a nodule in the prostate is not exactly what it is considered to be.

I also wonder about the term "clean" perineum. I am not so sure that such a thing exists.

Dr. Chute took this license, and may I? Just a word about this question of these stones in the faulty bag situations. We see quite a few of these because we don't use new bags for every resection. We blow a lot of them out. When we see them, all we do is tell the patients that we have to cystoscope them under anesthesia to see

what is in there. We put in a lithotrite, crush it, and take it out. When they wake up, it is gone. All these stones that are formed on faulty bags are so soft that they almost can be crushed with the hand. No matter how big they are, one can give them a bite with a lithotrite. It's like an atomic explosion. You look in there, and all there is is powder in the bladder. You can pull the piece of bag out with a forceps. It seems to me that suprapubic cystolithotomy shouldn't be necessary in very many cases.

One other thing: I'm pleased that Dr. Valk is using external urethrotomy in 23 per cent of cases. I am personally using internal urethrotomy in at least 25 per cent of cases, and I think it must be done if you are to avoid stricture.

DR. HARTWELL HARRISON (Boston, Mass.): Dr. Emmett, did you have any complications? (Laughter)

DR. EMMETT: We had one death. You remember my mentioning the death that we had, which was due to anuria. I don't know why, unless in the early experience someone put a needle up in the peritoneal cavity somewhere. We couldn't find it at autopsy.

We have had some gross hematuria, transient things that didn't amount to anything. We have had a few cases of urinary infection, some with dysuria, some with fever—maybe three or four—but they responded promptly to gantrisin.

Without sending letters of inquiry to patients, we have no correspondence to indicate that anybody had any serious trouble after they went home.

DR. HARRISON: You didn't have any acute perineal sepsis in the hospital?

DR. EMMETT: No. We had no patient, for instance, who had to be sent back to the hospital for care of any trouble. Of course, we did all these cases in the hospital. We had a urethral catheter indwelling for 24 hours on all patients.

When I go back, I think maybe we will start using one of the antibiotics, according to Dr. Leadbetter's suggestion. I think it might be preferable to just relying on gantrisin.

I still think, regarding Dr. Goodwin's suggestion about perineal versus transrectal biopsy, that anybody can do a good transrectal biopsy, but it takes experience and adeptness to get to the point where you really can put that needle where you want to through a deep perineum. I think anybody will agree with that.

PERCUTANEOUS ASPIRATION OF SELECTED EXPANDING RENAL LESIONS

JAMES H. DEWEERD

From the Section of Urology, Mayo Clinic and Mayo Foundation, Rochester, Minn.

A quick glance through the urologic literature of the past decade or two will serve to point up the well-established fact that the differential diagnosis and treatment of renal masses have been, and probably will continue to be, of major concern to the urologist. His concern is sharply focused on the fact that surgical extirpation of the malignant renal lesion continues to be the only really effective measure at his disposal.

Complete review and classification of the various expanding lesions of the kidney are not within the scope of this paper. To simplify the problem and to avoid significant deviation from its practical aspects, I shall define an expanding lesion as one that enlarges the kidney or its outline locally or generally and often causes minor or major distortion of the collecting system, but not one that develops locally or generally from obstruction of the collecting system (hydronephrotic enlargement). Further, I shall assume that most expanding malignant renal lesions or masses are solid ones, that is, adenocarcinomas, beginning in the renal cortex and commonly, although perhaps incorrectly, called hypernephromas. Benign expanding lesions are mainly cysts, commonly referred to as serous cysts. These may be single, multiple, multilocular or present in such numbers as to be included in the polycystic group or "syndrome." There are obvious areas of overlapping of these proposed categories, such as cystic or avascular necrotic degeneration of hypernephroma or conditions adjudged to be "cysts with malignant lining epithelial changes." I shall consider this overlapping later.

I have referred to the obvious need for surgical extirpation of all operable malignant expanding renal lesions. Some have thought that all expanding renal lesions should be explored and that the simple or serous cyst, or at least its free wall,[1, 2] should be excised because of local pressure phenomena, destruction of renal cortical tissue, danger of infection, associated hypertension, danger of rupture and hemorrhage, and the possibility of carcinoma in the walls, or associated carcinoma. However, the main concern seems to be, and rightfully should be, the urologist's inability to be certain that the lesion is a cyst and not a malignant tumor. It would appear further that, except when pressure causes symptoms or urographic evidence of obstruction and therefore parenchymal damage or when infection, hypertension or hemorrhage enters the clinical picture, the justification for surgical attack on any given simple serous cyst lies in the production of irrefutable evidence that the lesion is benign and not malignant.

DIAGNOSTIC CONSIDERATIONS

I shall not belabor the matter of differential diagnosis between cyst and tumor. The literature is replete with recounts of the urographic features of each.[3-5] One would be inclined to conclude that the gamut of procedures including excretory urography, retrograde pyelography, aortography and intravenous arteriography, nephrography and nephrotomography, when coupled with the clinical appraisal, should produce the diagnosis, as indeed it will in many cases. Diagnosis often depends not on the clinical and laboratory findings set down in rote fashion like pieces in a puzzle, but on the urologist's experience and acumen. In many situations of any given total, the clinical and laboratory findings plus an excretory urogram will suffice to permit a categoric conclusion that a given lesion is a renal neoplasm and that surgical intervention is indicated. The information produced by the retrograde pyelogram has enabled and will continue to enable the urologist to add to the

[1] Prather, G. C.: Surgical treatment of serous cyst of the kidney. J. Urol., **77:** 14–18, 1957.

[2] Clarke, B. G., Goade, W. J., Jr., Rudy, H. L. and Rockwood, Lawrence: Differential diagnosis between cancer and solitary serous cyst of the kidney. J. Urol., **75:** 922–929, 1956.

[3] Ochsner, H. C.: Cysts of the kidney. Am. J. Roentgenol., **65:** 185–199, 1951.

[4] Shivers, C. H. deT. and Axilrod, H. D.: A clinical comparison between benign solitary cysts and malignant lesions of the renal parenchyma. J. Urol., **79:** 363–367, 1958.

[5] Prather, G. C.: Differential diagnosis between renal tumor and renal cyst. J. Urol., **64:** 193–199, 1950.

number of cases in which he would do an exploration without further specific examination. At this point of the investigation a large percentage of any given number of lesions must be categorized as being either a cyst or a tumor, and only in the rare case does one have the courage to state dogmatically, "this is a renal cyst, I advise observation." Interest and experience enable us to state a preferred diagnosis, but each of us can point to cases in which our most considered opinions have been wrong. It is this experience, I am sure, that has induced leading urologists to decree that "solitary cysts deserve exploration."[1, 4, 5]

Aortography promised for a time to aid in the distinction between tumor and cyst. However, several inconclusive results and experience with false-negative reports dampened the enthusiasm that my colleagues and I may have had for this procedure. Recently, we have improved our technique and have greatly increased the use of intravenous arteriography and nephrotomography which, we believe, will prove more informative and reliable than translumbar aortography. Recent experience with a false-negative report, however, has served to renew my caution in interpretation and evaluation of nephrotomograms.

The controversial procedure that is the subject of this presentation is not new. Twenty-two years ago, Dean[6] reported his experience with aspiration in 150 cases of renal tumor. He reported no ill effects and recommended aspiration of renal cysts under local anesthesia, as he had done in 15 patients. In 1951, Ainsworth and Vest,[7] believing that exploration was neither necessary nor desirable in most instances of so-called cortical cyst, reported their excellent results with needle puncture as an office procedure in more than 20 cases of large renal mass in which cyst was strongly suspected. Only one tumor was encountered in their series. Lindblom,[8] in 1952, reported the aspiration of 80 renal lesions under local anesthesia, this being done simultaneously with excretory urography or retrograde pyelography. Forty (50 per cent) of the lesions were cysts, 34 were renal tumors, three were pararenal tumors and three were normal renal structures; during the same period, 59 patients were operated on without aspiration, representing 55 hypernephromas and four pelvic tumors. Nineteen years ago, Wheeler[9] reported the aspiration of two renal cysts under anesthesia.

My personal interest in this procedure was stimulated in 1955 when I was confronted with the problem of an asymptomatic, accidentally discovered renal mass in the 70-year-old mother of a medical colleague. All evidence pointed to the probability of renal cyst. The patient, anxious to avoid an operation, was content to let the matter rest there, but the physician-son as well as his brothers and sisters, realizing that there was still some uncertainty about the diagnosis, was loath to allow a shadow of doubt to obscure the future of his remarkably well-preserved mother. The resolution of this doubt for all concerned by aspiration of the lesion under anesthesia was highly satisfactory.

SELECTION OF PATIENTS AND PERFORMANCE OF PROCEDURE

Being mindful of the criticism leveled against aspiration procedures, I developed a modus operandi that to me seems logical and sound, provides maximal security with minimal risk, and avoids the morbidity, risk and expense incident to surgical exploration. The criteria that were gradually evolved and rather firmly adhered to, to provide a carefully selected group of patients for aspiration, are as follows:

1) An expanding renal lesion which urographically (a) is solitary, (b) does not jeopardize renal function by obstruction, excessive distortion or compression, and (c) conforms to urographic findings consistent with a solitary cyst.

2) Such an expanding lesion in a patient who (a) has not had asymptomatic gross hematuria, (b) has no symptoms referable to the upper part of the urinary tract, (c) has no increase of the erythrocyte-sedimentation rate, (d) has no signs or symptoms of occult malignant tumor, (e) has reached middle age or is older, and (f) has other problems (eye, orthopedic, and so forth) for which an elective operation hinges on resolution of the renal diagnosis.

[6] Dean, A. L.: Treatment of solitary cyst of the kidney by aspiration. Trans. Am. A. G-U Surg., **32**: 91–95, 1939.

[7] Ainsworth, W. L. and Vest, S. A.: The differential diagnosis between renal tumors and cysts. J. Urol., **66**: 740–749, 1951.

[8] Lindblom, K.: Diagnostic kidney puncture of cysts and tumors. Am. J. Roentgenol., **68**: 209–215, 1952.

[9] Wheeler, B. C.: Use of the aspirating needle in the diagnosis of solitary renal cyst. New Eng. J. Med., **226**: 55–57, 1942.

In such a situation I acquaint the patient with his problem and tell him that although the lesion may be either a tumor or a cyst and although I strongly favor the latter diagnosis, I cannot be certain.

The procedure is as follows:

1) Patient is hospitalized and prepared for exploration of the kidney.

2) Patient is anesthetized, positioned and draped for renal exploration (fig. 1).

3) Preliminary percutaneous aspiration of renal lesion is done (fig. 2).

4) Diagnosis of simple serous cyst is made if (a) crystal-clear (usually light-yellow) fluid is obtained in quantities of 15 cc or more, (b) Papanicolaou stain of centrifuged specimen of fluid fails to demonstrate malignant cells, and (c) injection of contrast medium demonstrates cystic space conforming with urographic deformity of expanding lesion without intracystic filling defects (fig. 3).

5) Intermediate incision and exploration of the kidney are done if (a) blood, (b) bloody fluid, (c) cloudy or turbid fluid, or (d) tissue or debris is aspirated.

FIG. 1. Position of patient for aspiration and possible exploration through flank.

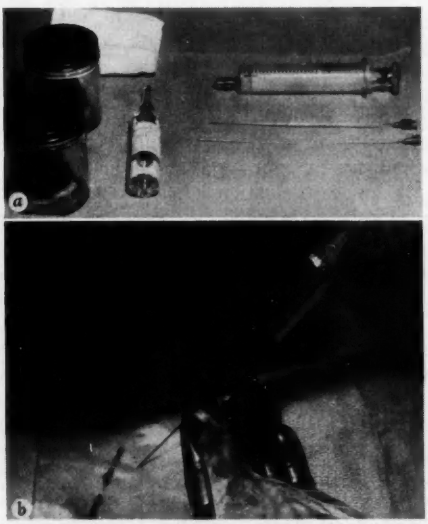


FIG. 2. *a*, Equipment includes 25 cc syringe, 6 inch 20 gauge needles with obturator, and urographic medium. *b*, Successful aspiration produces crystal-clear, light-yellow fluid in quantities of 15 cc or more.

OBSERVATIONS

During the 6-year period 1955 through 1960 I followed this general scheme of selection and treatment in 212 cases of renal mass. Exclusion of

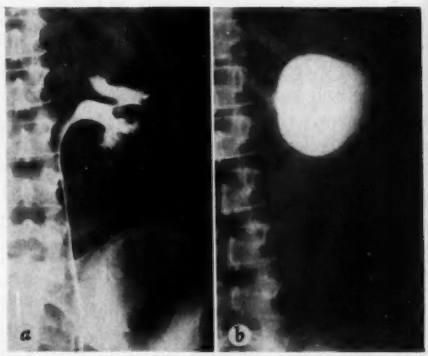


FIG. 3. Large smooth-walled cyst of upper pole confirmed by roentgenogram made after injection of contrast medium.

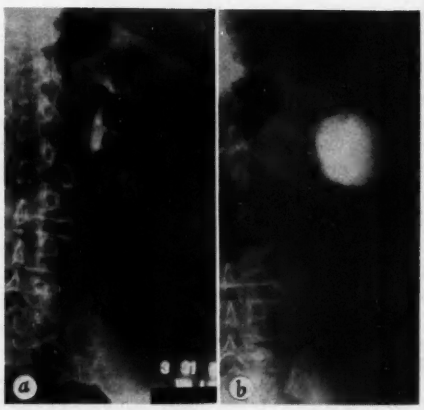


FIG. 4. *a*, Urographic deformity caused by small expanding lesion of left kidney is evident. *b*, Opaque medium outlines cyst.

19 cases of tumor originating in the renal pelvis, 12 cases of Wilms tumor, and 2 cases of angiolipoleiomyoma leaves 179 cases which are made up of 101 cases of renal cyst and 78 cases of renal adenocarcinoma.

Fifty-nine, or 33 per cent, of the 179 cases were considered suitable for attempted aspiration. In 42 of the 59 cases, a cyst (fig. 4) was diagnosed on the basis of the criteria outlined, and exploration was not done. In the other 17 cases, blood or bloody fluid, cloudy fluid, or debris was aspirated and immediate exploration revealed nine additional cysts. Two of the nine cysts were multilocular (aspiration had produced only a few cubic centimeters of clear fluid) (fig. 5), one contained crystalline material thought to be the result of ancient hemorrhage, and one was filled with old degenerated blood pigment (fig. 6). Blood-tinged fluid was obtained from the other five cysts. The blood was attrib-

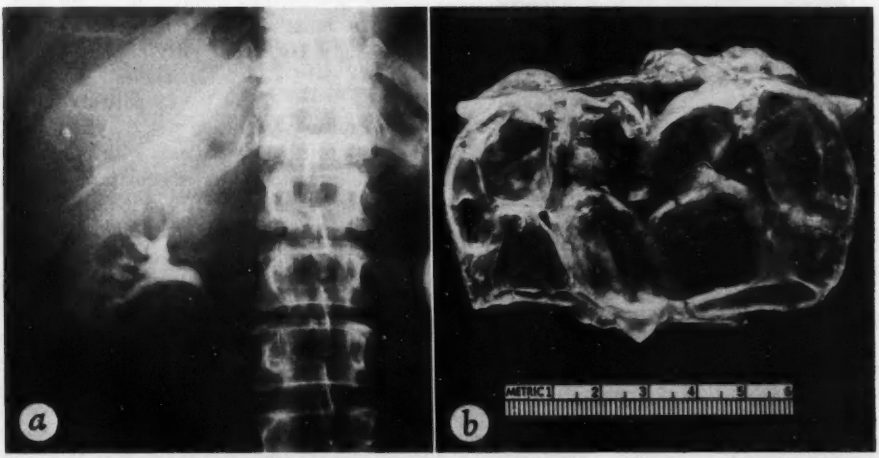


FIG. 5. *a*, Urographic deformity of calyces in lower pole. *b*, Multilocular cyst excised after aspiration had produced only few cubic centimeters of fluid.

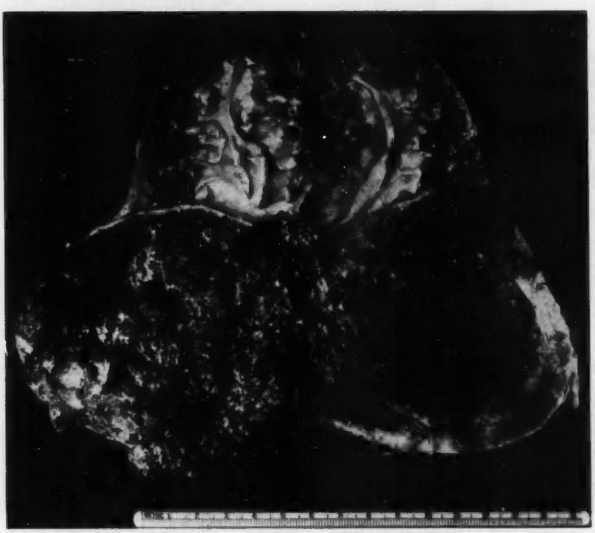


FIG. 6. Huge benign cyst, although asymptomatic, had been site of ancient hemorrhage.

uted 1) to passage of the needle through normal renal tissue before encountering the cyst as was true in 3 cases of intrarenal or subcortical cysts less than 3 cm. in diameter (fig. 7), or 2) to abrasion of the far wall of the cyst, which may occur in any case but is more likely when the cyst is small. In eight of the 17 cases, adenocarcinoma of the kidney was found and nephrectomy was performed after attempted percutaneous aspiration. In four of these 8 cases, special circumstances led me to disregard the established criteria for percutaneous aspiration, and failure to demonstrate a cyst came as no surprise.

FIG. 7. Urographic deformity caused by small intrarenal or subcortical cyst; aspiration failed.

One hundred and twenty, or 67 per cent, of the 179 renal masses were explored without preliminary aspiration. Fifty of these proved to be cysts and 70 adenocarcinomas.

The average age of the 59 patients subjected to preliminary aspiration was 61 years and the range 41 to 82. Five patients with proved renal cysts had a history of gross hematuria secondary to disease in the lower part of the urinary tract. One patient with asymptomatic gross hematuria had a recurrent stone in one kidney and a hypernephroma in the other. Only one patient had symptoms of distress referable to the kidney in question. He proved to have a hypernephroma. Twenty-one of 51 patients with proved renal cyst and four of eight patients with tumor

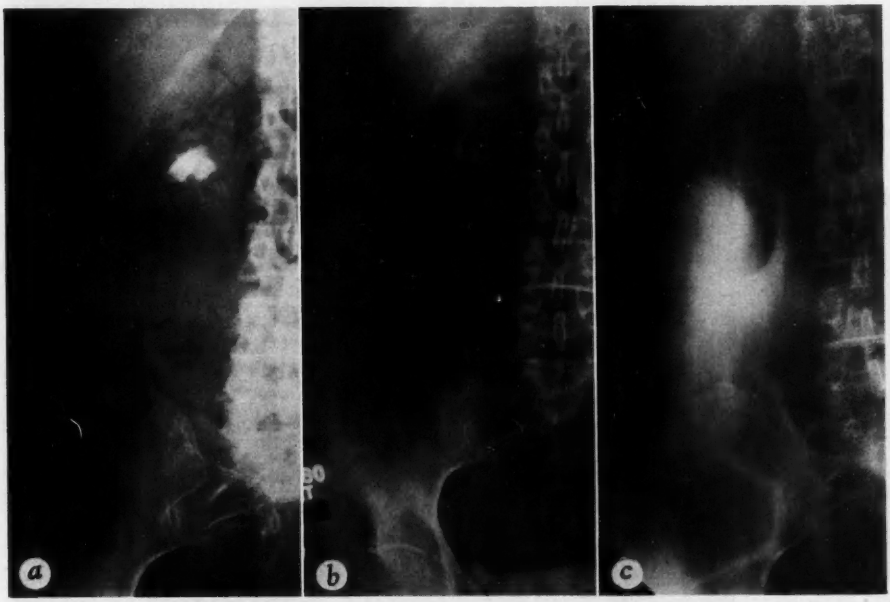


FIG. 8. *a* and *b*, Large right renal cyst disappeared after single puncture with aspirating needle. *c*, "Cystogram" demonstrates diffusion of medium outside cyst.

had microhematuria, grade 1 to 3, at the time of initial urinalysis. Two patients with signs of occult malignant tumor and grossly increased erythrocyte-sedimentation rate were found to have renal malignant tumor after unsuccessful aspiration.

Morbidity. Thirty-eight of 42 patients subjected to aspiration either left the hospital or were able to leave the morning after the procedure. One patient was readmitted because of chills and fever 24 hours later. Her illness lasted 36 hours. She subsequently has remained well without signs of renal infection. Two patients, both elderly and obese, complained of transitory tenderness in the opposite flank, apparently due to the exaggerated position on the operating table.

The 8 patients who proved to have carcinoma have been observed carefully for signs of recurrence in the flank. So far, none have had such a recurrence, four having been observed for more than 4 years. All are alive and well except a 75-year-old man who is quite debilitated.

COMMENT

I chose to perform percutaneous aspiration of selected renal masses with the patient under general anesthesia, rather than to perform it under local anesthesia as an office procedure, because 1) strict asepsis is available in the operating room, 2) optimal position is possible without discomfort to the patient, 3) apprehension on the patient's part is avoided, 4) the surgeon's maneuvers are not hampered by the patient's reactions and movement, 5) multiple attempts at puncture are quickly and easily made, 6) immediate surgical exploration follows unsuccessful puncture, thereby allaying the surgeon's apprehension concerning hemorrhage, continuing spread of malignant cells and the patient's worry that the test failed and operation for cancer is in the offing, and 7) risk of general anesthesia under present-day controlled conditions is minimal.

Although the procedure was intended to be purely diagnostic, the cyst disappeared after percutaneous aspiration in five of 14 cases in which appropriate followup studies are available (fig. 8, *a* and *b*). Presumably this is due to dissipation of the cyst fluid through the aperture made by the needle in the exceedingly thin cyst wall. Several "cystograms" in this series demonstrated diffusion of medium in the retroperitoneal tissues (fig. 8, *c*).

The risk of needling a mass and spreading carcinoma cells must be considered a real one, despite the reports by Dean and others and despite the present report. I do not advocate puncture of all masses, but do believe that, after careful evaluation of all aspects of each case, the risk that a malignant tumor may be needled is small—2 per cent when selective criteria were followed in this series.

Four of 70 kidneys operated on without preliminary aspiration were found to contain one or more small cysts occurring simultaneously with adenocarcinoma. These were unsuspected in that they caused no urographic deformity. Conversely, I do not believe that the possibility of finding an unrecognized, unrelated, coincidentally occurring carcinoma is sufficient reason for exploring a simple single cyst.

My personal experience and, to the best of my knowledge, the experience of others at the Mayo Clinic do not include a case wherein malignant disease was found in the base of a simple serous cyst that contained clear fluid. Rehm, Taylor and Taylor[10] recently described an apparent exception. Critical analysis of other reports of associated cyst and tumor seems to exclude them as points of refutation of the procedure being reported.

SUMMARY

Percutaneous aspiration of a carefully selected solitary expanding lesion of the kidney appears to have merit as a procedure that will provide an accurate diagnosis of renal cyst for a significant group of persons without the disability, morbidity and monetary burden imposed by surgical exploration. Fifty-nine (33 per cent) of 179 patients with an expanding renal lesion in this series were considered candidates for percutaneous aspiration, and 42 patients (23 per cent) of the series were spared exploration. Forty-two (71 per cent) of the 59 patients considered candidates for aspiration proved to have cysts that were successfully aspirated. The procedure would seem to find its greatest use in situations wherein specialized techniques, such as intravenous nephrotomography, are not available, cannot be utilized or fail to give a conclusive answer.

[10] Rehm, R. A., Taylor, W. N. and Taylor, J. N.: Personal communication to the author.

DISCUSSION

DR. T. LEON HOWARD (Denver, Col.): I would like to make a few remarks on this last paper from experience over many years, going back to the time when Hugh Young wrote his first book, YOUNG'S PRACTICE OF UROLOGY. If you remember, in the classification of tumors of the kidney at that time—the symptoms of the classifications rather—Hugh Young mentioned the fact that only 2 per cent of the patients with clear cell carcinomas had fever. We are now differentiating cysts from other tumors of the kidney, and I would judge, from what we have just heard, making a distinction whether a tumor is solid or cystic.

It has been my experience over all these years that I have never seen a patient with clear cell carcinoma of the kidney who did not have fever at some time if the temperature was taken regularly as a help in the diagnosis. I have never seen a case of clear cell cyst with fever. The thing that has impressed me greatly in the differential diagnosis of these two tumors, in addition to the other things you do—intravenous urograms, retrograde pyelograms, et cetera—is the fact that I have never seen a case of clear cell carcinoma of the kidney that did not have a high sedimentation rate. I don't know whether you people have run sedimentation rates.

There are many things that give you a sedimentation rate. Gout will give you a sedimentation rate. Tuberculosis will give you a sedimentation rate. But you are differentiating between a clear cell carcinoma of the kidney and a cyst of the kidney. You will never find a clear cyst of the kidney with a high sedimentation rate, and you will never find a clear cell carcinoma that doesn't have a high sedimentation rate. I have been doing sedimentation rates on these cases for many, many years.

Strange to say, I came upon a paper that was written in 1927 in which this same thing that I am stating to you now was advocated by a urologist who is long since dead.

If you take my advice, in differentiating these types of cases, you will never omit the evaluation of a sedimentation rate. It may be of great value to you in deciding whether to aspirate a kidney. I don't understand, though, why a doctor, if he is going to take out so many cubic centimeters, doesn't take it all out instead of letting it drain in the perineal space?

There is no question but what we have operated upon many cases of cysts needlessly. I think that many of these patients shouldn't be touched. They go through life with the greatest of ease. They will come to you because of a mass, maybe; but many of these patients don't need anything done to them—especially these old people whose only symptom is a heaviness there. I have a great many patients with cysts now who are walking the streets of Denver and surrounding country. We haven't operated upon them; and yet we have apparently made a correct diagnosis.

Run a sedimentation rate on these cases, and you will be astounded what a big help it is to you.

DR. JOHN K. LATTIMER (New York, N. Y.): We too have had the mother of a medical colleague who had a mass in the flank which qualified under all of the criteria listed here. We did a nephrotomogram and an aortogram. It delineated what appeared to be a cystic mass and was indeed a cystic mass. But we did explore it; and when we opened it very cautiously, there was papillary carcinoma within the cyst. As Dr. DeWeerd has said, these cysts do drain out through the hole you make, the needle puncture. All of us have done this on the operating table and have seen them ooze right under our eyes. In the cases where a papillary carcinoma is present in the cyst, you are going to get dissemination of papillary cells. As was brought out yesterday in the discussion, this is a highly implantable tumor. Our own bladder carcinomas, in the old days, used to implant 12 per cent in the wounds even when we were trying to avoid it.

In analyzing our figures, we discovered that not only did we have a number of carcinomas within cysts of the papillary type, but we had a total of over thirty cyst carcinomas of a solid type which at some time probably had a cystic factor. As Dr. DeWeerd says, the percentage may only be 2 per cent that you are going to run into trouble with tumors; but for that particular patient, the mortality might well be 100 per cent.

We have a rule at our place as a result of this experience. We will no longer aspirate any of these masses if doubt is present. If they are not operable, we will sit tight, as Dr. Howard says.

DR. GEORGE W. FISH (New York, N. Y.): As my grandfather walked across the plains in '49 to California from New York, I sort of walked across the cystic plain, I believe, in '38 and '40 when we reported a series of solitary cysts of the kidney. Among our cases were two that we thought from every point of view were inoperable, so we decided to find out, if we could, a little bit about what happens in the cysts. We aspirated them, injected air, and then watched them over a period of time. We found that fluid reformed in the cyst up to its full capacity that it had had before. We made contrast pictures with the air and the fluid levels and so on.

As Dr. DeWeerd says, if they have no symptoms and you are sure they are cysts, why do you do anything? I would like to have that question answered.

As Dr. Lattimer pointed out, in several of ours that appeared to be cysts from every point of view with the diagnostic things that have been done, when they were explored there was a tumor. With that, I would like very much to have Dr. DeWeerd answer the question: If they are harmless, why do anything about them?

DR. HENRY M. WEYRAUCH (San Francisco, Cal.): I would like to ask whether there is any virtue in decapitating or removing cysts. Are factual data available on what happens to them? Do they go on and destroy the kidney?

DR. GEORGE W. FISH (New York, N. Y.): I want to ask Dr. DeWeerd if he had used any clear sclerosing material to prevent the reformation of fluid? We did that on 2 cases with 50 per cent glucose, and there was no reformation or filling of the cyst.

DR. DEWEERD: Somewhere during the course of this presentation I used the word "controversial." I should have said it louder. I knew this would be, and I hoped it would be. I do feel that this is a thing that can be debated back to and fro.

It is a kind of procedure that you have to—at least I had to educate myself to and convince myself that I was doing the right thing. During the period of time that I used it, I was convinced—and I still am. At the moment, I should repeat that currently we are using nephrotomography in an increasing number of cases and are relying on it. However, not too long ago we had a false negative following an intravenous nephrotomogram.

As Dr. Fish pointed out and Dr. Howard pointed out, there are certainly pitfalls in any procedure that you are going to use, including exploration of the kidney unless at the time of exploration you very meticulously take biopsies from these various areas in the cyst wall. The report that Rehm and Taylor have brought out demonstrated that this cyst wall which they sent into the laboratory, feeling it was simple and benign, produced sheets of cells which were clear adenocarcinoma type. In a subsequent study in the laboratory, the patient was reoperated and the kidney removed.

With regard to Dr. Howard's remarks concerning the sedimentation rate, I do not have the figures on just how many of these patients had sedimentation rates performed; but a large percentage—the majority of them, I am sure, did have. We use the test a great deal.

Dr. Howard would be interested to know that the patient whose case I showed, the hypernephroma, had a normal sedimentation rate. Our tests may have been wrong, Dr. Howard, I admit; but our laboratory reported it to be.

DR. HOWARD: You must have had a very small tumor, then.

DR. DEWEERD: The tumor was this big around. (Indicating)

DR. HOWARD: He should have had a sedimentation rate.

DR. DEWEERD: The patient came to us with a psychosexual problem.

Dr. Howard's second question borders on the question that Dr. Harrison passed across the chairs to me and also Dr. Fish's question regarding emptying the cysts. I must re-emphasize that we made no attempt to empty the cysts or to drain them completely. We were doing this strictly as a diagnostic procedure. This is based on the contention that the great majority of these tests are innocuous insofar as the patient's health is concerned.

You will also recall that if any of these patients had any systems referable to this kidney—heaviness in the side, pain, palpable mass—they were subjected to operation.

You recall that 50 were operated on primarily without preliminary percutaneous aspiration.

With regard to my ability to say that this is a cyst, I will observe it. I almost categorically refuse to do that, because I cannot honestly prove to myself and to the patient's satisfaction that a given lesion is a cyst, whether you use the translumbar aortogram or whether you use the

urogram with the catheter in the artery, whether you use the intravenous nephrotomogram. We have examples in all cases where the report has been a false negative.

I'm sorry I don't have the slide which shows the case where five members of our staff repeatedly called it a cyst until we did an aortogram. This dates back about six years ago. We finally did an aortogram and found that this very slowly increasing thing was indeed an adenocarcinoma. This case is reported in a paper that I presented some time ago in which the polycythemia was related to kidney tumors in a group of 8 cases.

Dr. Harrison's questions about the refilling of the cysts: These 5 cases that I mentioned have not refilled, to the best of my knowledge. One of them had a series of excretory urograms made on the occasion of return over a four-year period. He is the kind of patient who wants to be examined from head to toe each time. He wants to make sure that his kidney is all right. He is the only one who has had more than one excretory urogram. His cyst has not recurred.

Regarding the recurrence of cysts, in my experience I have seen one instance where a patient was operated on in our clinic by one of our colleagues for a simple cyst. The cyst wall was excised. I had occasion to see this patient 3 months ago. An excretory urogram had been done for one reason or another. I don't remember the incident. Comparing the pre- and postoperative films, one couldn't tell the difference. I don't know what happened in this case. I am sure this surgeon, having done a great deal of urologic surgery—not a member of our department—is perfectly capable of excising a free wall of a cyst, which his operative note says he did. But this cyst apparently had reformed.

In reference to Dr. Lattimer's question, I would ask him, is this cyst that you referred one which contained clear fluid?

DR. LATTIMER: Yes, it did.

DR. DEWEERD: I think I would have made a mistake on that one.

I think I would also argue a little bit about the choice of papillary carcinoma and the differentiation of tumor cells. I am not a pathologist; but if it was papillary carcinoma, I wonder if the lesion in question did not at one time or another have a connection with the collecting system of the kidney.

DR. LATTIMER: I think this is a well enough established entity. It occurs enough of the time. You can have a single cyst with papillary carcinoma in it, and not necessarily a communication.

DR. DEWEERD: We have never seen one. We have seen lots of cystic hypernephromas. We have seen lots of hypernephromas which have undergone cystic degeneration. They will have cloudy fluid in them. They will have turbid fluid in them. They will have bloody fluid in them. According to the criteria which I have established for myself, these would be operated on.

PSYCHOSOMATIC "CYSTITIS"

DONALD R. SMITH

From the Division of Urology, University of California School of Medicine, San Francisco 22, Cal.

If a patient complains of urinary frequency this does not necessarily mean that the patient has organic urologic disease. As some of my readers will recall, when faced with final examinations in school, acute anxiety may cause transient vesical irritability. I have studied psychosomatic urinary problems for the past 20 years and have found that about 10 per cent of my patients who complain of urinary frequency are merely the victims of their own emotional tensions.

Though there is surprisingly little in our current literature[1-11] dealing with the influence of the psyche on urinary function, a Chinese proverb, many centries old, states that "the bladder is the mirror of the soul." Therefore, this concept is obviously not new.

Experimental and clinical observations will be presented which readily explain the symptomatology of psychogenic bladder dysfunction. Three different psycho-physiologic mechanisms may cause abnormalities in urinary function: 1) acute spastic bladder reaction; 2) variations in excretion of salt and water, and 3) the fetish of polydipsia. The physiologic response is different in each, and each in turn can cause symptoms quite different from those resulting from organic disease.

THE PSYCHODYNAMICS OF VESICAL FUNCTION

The influence of the emotions on vesical activity. Mosso and Pellacani[12] in 1881 were the first to utilize cystometry in the study of vesical physiology. In both animals and human subjects, they observed involuntary contractions of the detrusor muscle in response to psychic stimuli.

In 1949, Straub, Ripley and Wolf[13, 14] recorded the neurovesical reactions by means of cystometry in 26 neurotic patients who suffered from psychogenic urinary difficulties. An indwelling catheter was placed and 50 to 200 ml. water was instilled into the bladder. The catheter was then connected to a recording cystometer. They found that inconsequential conversation caused no abnormality in vesical tone. Subjects to which the patients were sensitive were then discussed and a marked increase in detrusor tone was observed. Finally, diverting conversation (or the administration of intravenous barbiturates) resulted in a return to normal resting pressure. These observers noted two types of vesical reaction: hypermotility and hypomotility. In the latter, vesical atonia and even acute urinary retention were noted.

Hypermotility was observed in 18 (70 per cent) of their patients. The history and cystometric response of one of their subjects are summarized.

A 28-year-old man complained of urinary urgency and frequency, fatigue and premature ejaculation. He had had an unhappy childhood and his parents had continually quarreled. He developed hostility toward his father and felt sorry for his mother. As he grew up she became

[1] Auerback, A. and Smith, D. R.: Psychosomatic problems in urology. Calif. Med., **76:** 23–26, 1952.

[2] Clancy, F. J.: Urologic symptoms of psychogenic origin. Urol. & Cutan. Rev., **37:** 703–707, 1933.

[3] Cone, R. E.: Psychosomatic problems in urology. J. Urol., **56:** 146–150, 1946.

[4] Green, M. R. and Dean, A. L.: Some psychiatric aspects of symptoms of genito-urinary disease. J. Urol., **72:** 742–747, 1954.

[5] Menninger, K. A.: Some observations on the psychological factors in urination and genito-urinary afflictions. Psychoanalyt. Rev., **28:** 117–129, 1941.

[6] Chertok, L., Aboulker, P. and Cahan, M.: Perspective psychosomatiques en urologie. Evolut. Psychiat., **3:** 457–475, 1953.

[7] Smith, D. R.: Psychologic aspects of urology in women. G.P., **8:** 57–61, 1953.

[8] Smith, D. R.: General Urology, 3rd ed. Los Altos, Cal.: Lange Medical Publications, 1961, chapt. 28.

[9] Smith, D. R. and Auerback, A.: Functional diseases. In: Encyclopedia of Urology. Berlin: Springer-Verlag, 1960, vol. 12, pp. 1–20.

[10] Williams, G. E. and Johnson, A. M.: Recurrent urinary retention due to emotional factors. Psychosom. Med., **18:** 77–80, 1956.

[11] Knox, S. J.: Psychogenic urinary retention after parturition, resulting in hydronephrosis. Brit. Med. J., **2:** 1422–1424, 1960.

[12] Mosso, A. and Pellacani, P.: Sur les fonctions de la vessie. Arch. ital. de biol., **1:** 97–128, 291–324, 1882.

[13] Straub, L. R., Ripley, H. S. and Wolf, S.: Disturbances of bladder function associated with emotional states. J.A.M.A., **141:** 1139–1143, 1949.

[14] Straub, L. R., Ripley, H. S. and Wolf, S.: An experimental approach to psychosomatic bladder disorders. New York State J. Med., **49:** 635–638, 1949.

increasingly dependent upon him. When he was discharged from the Army and returned to his family, he experienced fatigue and vesical irritability.

A cystometric study was obtained according to the technique just described. After the instillation of 150 ml. water, the examiner began to discuss the patient's childhood. Intravesical pressure was not affected. When, however, his family problems were brought up, involuntary detrusor contractions occurred and intravesical pressure rose to 30 cm. water. Diverting conversation then caused the pressure to return to normal. When his financial, family and marriage problems were again discussed, his bladder again became tense and again pressures up to 30 cm. water were recorded.

Psychotherapy revealed many conflicts regarding his mother, whom he actually resented. At the end of 2 months of treatment, his urinary frequency had disappeared. This type of vesical reaction was typical of the group and was associated with general tension, anxiety and resentment. These patients usually note frequency and urgency in the forenoon; they pass small volumes of urine. Comparable nocturia is absent.

The influence of the emotions on the renal excretion of water and salt. Blomstrand and Löfgren[15] studied the effect of the emotions on the renal circulation. They observed that emotional stress could cause either abrupt diuresis or antidiuresis. They cited the work of Bykow and Alexjew-Berkman who had dogs drink water under certain fixed circumstances, thus establishing a conditioned reflex. Later, the same environment caused diuresis without administration of the water.

Blomstrand and Löfgren placed 4F catheters at the level of the renal arteries (via the carotid artery). In three control animals, India ink was injected into their catheters and the kidneys were immediately removed. Seventeen additional cats were then confronted by a barking dog. India ink was immediately injected into their catheters and the animals were sacrificed.

The control group had more pigment in the renal cortices than in the medullary zones. The kidneys of the frightened and enraged animals, on the other hand, showed varying degrees of blanching of the cortices and increased staining of the medullary portions. Microscopically, these kidneys revealed glomerular ischemia caused by spasm of the afferent arterioles. Such a reaction would, of course, cause oliguria.

[15] Blomstrand, R. and Löfgren, F.: Influence of emotional stress on the renal circulation. Psychosom. Med., **18:** 420–426, 1956.

TABLE 1. *The effect of stress on urinary output (renal blood flow? antidiuretic hormone?)*

Emotional State	Urine ml./4 hrs.	Sodium meq./4 hrs.
Tranquility	170	28
Restless and tense	58	3
Tranquility	200	20
Intense anger	621	80

These workers concluded that this psychogenic renal cortical ischemia was activated by increased secretion of epinephrine. However, Verney[16] has shown rather convincingly that emotional stress also acts through the hypothalamus to affect the secretion of antidiuretic hormone, thus causing either diuresis or antidiuresis. He stated that these effects were not secondary to changes in renal blood flow or adrenal hormones.

Clinical observations made by Schottstaedt, Grace and Wolff[17] bear out these experimental observations. They studied the rates of water, sodium, potassium and creatinine excretion in 5 people in both tranquil and stressful situations. They found that under normal conditions little variation in excretion of the aforementioned substances was observed from day to day. However, when these patients were subjected to emotional upset, gross alterations in excretions of water and electrolytes were observed.

Table 1 shows the typical reactions of oliguria and diuresis which were recorded in two of these patients when subjected to various types of psychic stress. If tension (or listlessness) developed, significant oliguria immediately supervened. When tranquility returned, the inevitable diuresis was observed. But if deep feelings of anger (or apprehension) were experienced, immediate and significant diuresis occurred.

These experimental and clinical observations demonstrate that different emotional states can cause either diuresis, or fluid retention and

[16] Verney, E. B.: Some aspects of water and electrolyte excretion. Surg., Gynec. & Obst., **106:** 441–452, 1958.

[17] Schottstaedt, W. W., Grace, W. J. and Wolff, H. G.: Life situation, behavior patterns and renal excretion of fluid and electrolytes. J.A.M.A., **167:** 1485–1488, 1955.

TABLE 2. *Differential diagnosis of organic and psychosomatic "cystitis"*

Etiology	Frequency all day	Frequency part of day	Nocturia	Urgency	Volume of each voiding	Fluid intake	Recurrent edema
Bacterial cystitis	Yes	No	Yes	Yes	Small	±	No
Acute spastic bladder	No	Yes	No	Yes	Small	±	No
Diuresis	No	Yes	No	No	Large	±	Yes
Polydipsia	Yes	No	Yes	No	Large	High	No

oliguria followed by diuresis. The type of response and its degree depend upon the emotional reactions of the person. The mechanisms for water retention or diuresis are activated by changes in renal blood flow or excretion of posterior pituitary hormone.

Jules Janet[18] in 1890 wrote a classical monograph entitled Les Troubles Psychopathiques de la Miction. He quoted his chief, Guyon, as having said: "It is easy to differentiate between psychic cystitis and true cystitis, for patients suffering from the former disease pass a large volume of clear urine." He was describing the phase of diuresis.

The patient suffering frequency induced by this mechanism has attacks lasting only a few hours, usually in the morning. He voids large volumes of pale urine. This may reflect immediate diuresis initiated by sudden anger or it may represent the diuretic phase following antidiuresis which was initiated by feelings of listlessness or anxiety experienced on the preceding day.

One of my colleagues has observed that while under stress, he gains as much as 11 pounds (5 liters of water) in 48 hours. During this period he has oliguria and peripheral and facial edema. When the stress is relieved marked diuresis (with frequency) occurs and his weight rapidly returns to normal.

Polydipsia. A third cause of urinary frequency is an excessive intake of fluid, which may not be consciously recognized by the patient. He may confuse the psychosomatic symptom of a dry throat with thirst which he therefore seeks to quench. Many people drink large quantities of fluid to flush out the kidneys, which they consider in the same light as the bowel. Frequency, in this instance, is physiologic, but the cause of of the polydipsia is not.

[18] Janet, J.: Les troubles psychopathiques de la miction. Essai de psychophysiologie normale et pathologique. Paris: Librairie le Francois, 1890.

These patients may suffer frequency night and day, but they admit that the volume of each voiding is large in contradistinction to the acute spastic bladder reaction (or bacterial cystitis) in which the voidings are scanty.

A remarkable example of polydipsia is a woman whom I saw over a period of 3 years because of diurnal frequency and nocturia. Urologic examinations were repeatedly normal. She denied that she drank fluids excessively. Finally, I requested that for 48 hours she record the time and volume of each fluid increment taken and the time and volume of each urination. Her tabulation revealed a fluid intake of 5 liters per 24 hours; the volumes of her voidings ranged from 13 to 17 ounces! Thus was unfolded the simple answer to her severe frequency.

CLINICAL FINDINGS

The clues to the differential diagnosis between organic and psychosomatic cystitis are uncovered by careful history-taking (table 2).

Diurnal frequency. It is essential to ascertain whether the frequency persists all day or lasts for only a few hours; whether it occurs every day or is periodic; and whether large or small volumes of urine are passed. There is a constancy in urinary symptoms in organic vesical disease. Contrariwise, it is typical for the emotionally disturbed patient to have frequency for only a few hours a day, usually in the morning. These attacks are sporadic; they may be present one day and absent the next.

Organic frequency or the acute psychosomatic spastic vesical reaction is associated with small voidings, but in the presence of diuresis or polydipsia, urinary volumes are normal.

Nocturia. The main clue to the presence of psychogenic frequency is the absence of nocturia, which also implies that vesical capacity is normal despite frequent small voidings during the day.

Burning. Burning on urination is common in

true cystitis and may be experienced in psychogenic spastic bladder. Often, however, the discomfort is not related to the act of urination. It is vague, poorly localized and comes and goes without rhyme or reason. In both sexes, this type of complaint suggests a sexual component as an etiologic factor.

Fluid intake. If the patient has severe morning frequency, yet passes large volumes of urine, his fluid intake that morning should be ascertained. If it was minimal, diuresis is probably the cause. This can be readily established by having the patient weigh himself 3 times a day. Changes in body weight are directly proportional to changes in body water.

If polydipsia is denied but suspected, have the patient record the volume and time of each increment of fluid taken and the time and volume of each voiding over a 48 hour period.

Recurrent edema. The patient who has diuretic frequency preceded by a period of oliguria will, during the latter phase, note edema of the ankles, fingers and face. With the onset of diuresis, the edema disappears.

Sexual satisfaction. Patients with psychosomatic cystitis, through whatever mechanism, are uniformly sexually frustrated. It is on the morning after such an experience that their symptoms are most severe.

The event preceding the first attack. Women often report that frequency was first noted after some form of sexual trauma, such as rape, unsatisfactory intercourse, sexual temptation or worry over an impending marriage.

The examination of the patient with psychosomatic cystitis requires only brief discussion. The results of urinalysis are normal. Persistently low urinary specific gravity implies polydipsia. Cystoscopy usually shows no abnormality, but trabeculation secondary to external sphincter spasm may be noted.

The presumptive diagnosis of psychosomatic cystitis can be made from a carefully taken history. Absence of pus and bacteria in the urine and a normal cystoscopic appearance of the bladder should cause the physician to suspect that the urinary frequency may be psychogenic.

In women, the diagnosis can usually be made by merely asking what they think is the cause for their vesical symptoms. Most of them will ask, "Do you think it could be my nerves?" When the doctor says he has already assumed this to be true the patient usually replies, "You are the first doctor who would listen to me. My attacks always follow emotional upsets." Women understand the importance of the emotions in everyday living and are quite willing to accept this explanation as the cause for their frequency.

Men, however, are different. Their egos do not allow them to admit that they are not the masters of their tensions and anxieties. Therefore, they are more difficult to convince.

TREATMENT

The most important aspect of treatment is the physician's explanation of how "nerves" play tricks on the bladder. This immediately relieves some of their anxieties and thereby lessens symptoms.

The acute spastic bladder reaction may be suppressed by small doses of a sedative. Frequency caused by acute diuresis may be lessened by limiting salt intake. The polydipsic patient will be relieved if fluid intake is sharply reduced. Parasympathetic blocking agents have not been satisfactory in controlling the acute hypermotile bladder.

Empiric organic therapy is mentioned only to condemn it. Urethral dilatation, endoscopic applications of noxious chemicals to the urethra and trigone, prostatic massage and resection of the bladder neck are harmful because they convince the patient that he has some serious organic disease.

Psychotherapy is the definitive treatment for these patients, since in addition to their urinary symptoms they have psychosexual difficulties and deep and basic psychologic problems which cannot be solved in any other way. That a very large proportion of these patients have been relieved of their vesical and other neurotic symptoms by this means is further proof of the verity of these observations. This aspect of the problem will be dealt with in a subsequent report.

SUMMARY

Organic disease of the bladder is commonly mimicked by psychogenic mechanisms which influence vesical or renal function. Frequency of urination may, therefore, be caused by an acute spastic bladder reaction, diuresis or polydipsia. The most common symptom complex of psychosomatic "cystitis" is diurnal frequency without nocturia. The presumptive diagnosis can usually be made by taking a careful history.

DISCUSSION

DR. WILLIAM P. HERBST, JR. (Washington, D. C.): I agree with everything that Dr. Smith has said. There have been over the years innumerable examples of most profound psychochemical—and I would suggest "psychochemical" rather than "psychosomatic" as being possibly a little more scientific—phenomena, going back to the time of Mesmer and Charcot, who reported such physical phenomena, as for instance, the ability to produce acute blisters on the skin surface of patients by autosuggestion.

There is nothing more simple or impressive or yet a more definite example of psychochemical phenomena than fainting, the simple phenomenon of fainting.

The British neurologists have contributed in this field rather impressively, in the problem, for instance, of impotence. They have found, in the patients who have been so wrought up that they have done prefrontal lobotomy, before operation practically zero ketosteroids; following the lobotomy, an increase in ketosteroids and return of potency.

In Boston some brilliant contributions have been made in this field, one of which is the observation of the results of stress in the Harvard racing crew where the eosinophil count was taken on the crewmen, the cockswain, and the coach during practice at the Yale-Harvard race, with a tremendously impressive variation, which was uniform.

More recently, in the Transactions of the Laurentian Conference, there has been a very great contribution of—I can't think of his name at Walter Reed—concerning the relationship of stress to the hypothalamic influence on the general homeostatic pattern. We have the opportunity to observe many more such psychochemical relationships ourselves—and if any one of us would really take the time to skim the literature and accumulate for our own information the data that are available now, I am sure we would be astounded.

This paper of Dr. Smith's has been most interesting, most valuable. Among other things, it emphasizes the necessity which, in current medical practice, isn't observed to the extent that it should; namely, the reliance on clinical laboratory data rather than the time-consuming taking of a careful history.

DR. REED N. NESBIT (Ann Arbor, Mich.): I want to discuss this very interesting and important paper. There is a corollary to the bladder activity that is referred to. Dr. Smith has been discussing abnormal frequent urination on the excessive side. I refer to the abnormal infrequency of the urination that is sometimes caused by psychological factors. I only mention it to give balance to this thinking, so that the discussion should contain the thought.

Those of us who see patients who present themselves with urinary disorders ask how often the patient urinates with the idea of getting information regarding abnormal excessive frequency of urination. But sometimes we forget to make an inquiry regarding the infrequency of it. I think it is equally important or perhaps more important, physically, to get that information. The patient who has psychogenically an infrequent urination is very apt eventually to have infection, which will respond only when the psychological disorder has been relieved.

A case in point is a young child who was sent to us from the very northern part of the northern peninsula in our state because of urinary tract infections which she had periodically had for 8 years. She was 11 years old.

We put her through the gamut of studies and found no evidence of trouble. We sent her back to the referring physician, who was a pediatrician of great ability and sagacity. A couple of years later he returned the child to us with some pyelograms. He said, "See, she has abnormal pyelograms. I caught you this time." She did indeed. She had ureters that were dilated, but they were also abnormally separated. It was evident to me from looking at the pyelograms he sent with her that she had a distended bladder.

On inquiry, we found that this child indeed did have infrequent urination. In fact, she only urinated once every 24 hours.

Our psychiatrists found that she was a rejected child. There had been a broken marriage at the age of two and a half. Her mother remarried a man whom the child hated. This mother attached herself to the new husband and beat up the child because she wet herself at the age of three. Thereafter she urinated only once every 24 hours. She had an infection constantly.

One other instance is a patient whom we had

studied for hypertension. She had urinary tract infection and bilateral chronic pyelonephritis. One side of the pyelogram was much worse than the other side. Our hypertension unit asked us to take out the worst affected kidney, which we refused to do, of course. Dr. William Baum, then my associate, made the inquiry about her frequency of urination and found out that here was another child, about 16, who urinated only once every 24 hours. He corrected that situation.

Interestingly enough, her infection responded, but the pyelograms showed no improvement. Her hypertension disappeared, too.

I had a letter from one of my previous residents, who now lives in Long Beach. He said this girl still urinates by the clock.

Dr. Clarence V. Hodges (Portland, Ore.): I think to give this subject complete balance, we must allow the pendulum to swing all the way from the frequency that Dr. Smith described through Dr. Nesbit's infrequent urination to the patient who goes into acute psychogenic urinary retention. This is one of the problems that is most apt to result in unnecessary surgery, polysurgery, and the ultimate and extreme serious consequences that can follow.

I think one of the most interesting studies is that reported, Dr. Emmett, by Dr. Johnson (and I've forgotten the other author at your institution) on a patient with a very similar background (and I won't repeat it) to those previously described: rejection; being taught that urine was a poisonous thing, that it would kill grass, and that it must be done secretly and without even noticing the genitalia; going on to further psychic trauma by the stepfather's rape, and so on. It took 4 years of psychotherapy, I believe, Dr. Emmett, before this patient's spells of urinary retention, which were precipitated by the attentions of men, were brought under control. During this last year they could still be precipitated by relieving these episodes.

The point is that the patients—and these are always women except in two instances, I think, cited by a urologist with wartime experience—the women who go into retention yet have normal findings on cystoscopy should certainly be benefited by the physician's thorough acquaintance with the psychic side before being subjected to any type of endoscopic or open surgery for relief of this tension.

Dr. David M. Davis (Haverford, Pa.): In the interest of balance, I think we should also recall that it is quite possible and indeed frequent for people to have severe psychic troubles and also physical troubles. Such individuals can often be greatly benefited by relieving some of their physical troubles although their psychic troubles remain unchanged.

Dr. John L. Emmett (Rochester, Minn.): I will limit my remarks to just a therapeutic suggestion when it comes to psychogenic retention of urine in women, based on personal experience of a case. That is that psychotherapy is sometimes of great help.

We had this one patient who was cured by one treatment. We filled the bladder with contrast material and turned all the machinery on. The patient hadn't voided for 9 months. She had been catheterized and had an indwelling catheter for a period of time. Then we got her in this machine, you see. We had all the elaborate equipment. She wouldn't void. So I tried to help increasing the pressure in the bladder by massaging the bladder. I gave a shot of urocholine, and then I massaged the bladder again. Finally she let it all go. She had the feeling that the treatment cured her. It has been over a year, and she is voiding satisfactorily.

Dr. Donald F. McDonald (Rochester, N. Y.): Mr. President, would you take a poll of the members and find out how many have seen retention on a psychogenic basis, how many cases, and how many were female and how many were male patients.

President Rusche: We will ask for a raising of hands. How many have seen this phenomenon, and how many patients are females? [Show of hands.]

How many are males? [Show of hands.] There is quite a difference. Only six have seen males.

Dr. Donald R. Smith: I would like to point out how historic this concept is. There is a Chinese proverb, many, many centuries old, which states that the bladder is the mirror of the soul. This concept is quite old.

I didn't touch upon urinary retention. Certainly, this has been very well documented, as has been pointed out.

I would like to show one slide which shows a cystometrographic study on such a patient. [Slide] This little girl had an alcoholic mother. Her father died when she was very young. Her mother would sometimes indulge her children and the next day just kick the hell out of them. It was a pretty tough sort of situation.

She started to masturbate at about the age of 13. This averaged about twice a week, and persisted all the time except when she would have a new boyfriend, in which case she would desist. She was torn so often with a boyfriend who wanted to have a little doings tonight, and she felt like she sort of should, and then she chickened out in the end. One day she was going out with a boy. She was pretty sure what was going to transpire. She decided this time, "I will co-operate." When the chips were down, she just couldn't quite let herself do it. This left her so dejected, so ashamed, so overwhelmed, that she went into urinary retention. When she came into the clinic, her bladder was well above her umbilicus. Without draining her bladder, a catheter was inserted, and this cystometrogram taken. Only after two injections of sodium amytal could she finally start to masturbate in a rather unconscious manner. Wherupon her intravesical pressure rose. She said she felt swell and from that time had no further difficulty, although she was given some psychotherapy during the next 10 days.

You certainly see this situation very commonly. I would say that in any woman who has been voiding fairly well, then suddenly goes into acute retention, it can almost always be an acute psychosomatic reaction unless she happens to have multiple sclerosis or something of that sort.

This type of reaction is one of being completely overwhelmed by the world, whereas the other type I spoke of tends to be more the anxious, tense sort of business. I think it can be exceedingly well documented in this way.

NON-OBSTRUCTIVE VESICOURETERAL REGURGITATION

ROBERT A. GARRETT, ROBERT K. RHAMY AND JAMES R. CARR

From the Department of Urology, Indiana University School of Medicine, Indianapolis, Ind.

Vesicoureteral regurgitation has evoked much constructive controversy and investigation in recent years. That no unanimity of opinion either as to cause, effect or management has crystallized is evident by the recent proceedings of a panel of prominent authorities on this subject.[1] It is doubtful if this essay will settle the controversy, though it is hoped that it may further our knowledge in a phase of this problem. As early as 1903, Sampson[2] in an outstanding piece of work showing the oblique course of the intramural ureter, not only demonstrated the valve-like effect of this segment but also implied that the breakdown of this valve-like mechanism should be considered pathologic. Basic underlying causes for regurgitation are obviously numerous. Infravesical obstruction, neurologic deficit, and iatrogenic changes all may produce this disorder. Our study herein reported deals only with that controversial group of patients in whom no infravesical obstruction, or other known cause can be found. While some workers voice the opinion that obstruction lurks in these individuals as well, it is our purpose to submit evidence to the contrary. Further, this paper will attempt to set forth our experiences with patients of this type in regard to methods of diagnosis and their differentiation from patients with vesicoureteral regurgitation secondary to obstruction at or below the vesical outlet.

Non-obstructive regurgitation is referred to by a small group of authors[3, 4] as megacystis. These investigators feel that non-obstructive regurgitation is usually related to an excessively large bladder or trigone. Yet, the term megacystis does not imply regurgitation, nor is a large bladder always found in non-obstructive vesicoureteral regurgitation. Therefore, we do not regard the term megacystis as properly descriptive of the group of patients herein discussed. Criteria for this syndrome might be listed as 1) unilateral or bilateral vesicoureteral regurgitation, 2) absence of any signs of obstructive uropathy, and 3) lack of neurological deficit.

Our interest in this phenomenon stemmed from an investigation of the diagnostic merits of cinefluoroscopy in urologic disease. Early in the course of our studies it became evident that a significant number of children, in whom chronic or recurrent infection was found, displayed vesicoureteral regurgitation in absence of demonstrable obstructive changes at the infravesical level. Our diagnostic efforts and techniques were expanded to further characterize this small group of patients. The results of these investigations are set down in the report that follows.

MATERIAL AND METHODS

As a part of diagnostic workup for chronic or recurrent urinary tract infection, 149 patients, the vast majority of whom were children, were studied by cine-cystourethrography. Of these, 30 were found to have non-obstructive vesicoureteral regurgitation and constitute the basis for this report. Table 1 discloses a classification of these patients. All patients considered to have non-obstructive vesicoureteral regurgitation were subjected to the standard diagnostic maneuvers designed to rule in or out obstruction. All had upper urinary tract studies, usually excretory urography, and were evaluated as to changes secondary to obstruction and/or infection. Attempts were made to accurately evaluate residual bladder urine. Cystoscopic examination was done in each and efforts were made to evaluate the vesical orifice, the presence of vesical trabeculation, ureteral orifice patulousness and gross bladder capacity at physiologic pressure. Cystometrographic studies were done on many of these patients with particular emphasis on voiding pressure levels. Careful neurologic examinations were done in each to eliminate neurologic deficit as a cause for vesicoureteral abnormality. Urethral calibration was done in each and was considered normal.

This study supported in part by the Riley Memorial Foundation, and in part by U. S. Public Health Service Grant No. R.G. 7071.

[1] Panel on ureteral reflux in children. J. Urol., **85:** 119–144, 1961.

[2] Sampson, J. A.: Ascending renal infection. J. Hopkins Hosp. Bull., **14:** 334–349, 1903.

[3] Williams, D. I.: Megacystis and mega-ureter in children. Bull. N. Y. Acad. Med., **35:** 317–327, 1959.

[4] Paquin, A., Marshall, V. and McGovern, J. H.: The megacystis syndrome. J. Urol., **83:** 634, 1960.

TABLE 1. *Cine-cystourethrography for urinary tract infection (149 children)*

Bladder neck obstruction		56
With regurgitation	36	
Without regurgitation	20	
Normal cinefluoroscopy		41
Non-obstructive regurgitation		30
Other obstructions		7
Prostatic valves	4	
Meatal stenoses	3	
Miscellaneous regurgitators		12
Megalobladder without regurgitation		3
		149

INCIDENCE

Twenty-eight of the 30 patients herein discussed were females. The average age at onset was 4.32 years, the youngest being 3 months and the oldest 30 years. Twenty-eight were under the age of seven.

CLINICAL EVALUATION

The vast majority (29) of these subjects had recurrent urinary tract infections characterized by fever and pyuria on at least one occasion.

A 16-year-old boy was admitted to the hospital with epigastric distress having had no antecedent history of infection, but whose blood urea nitrogen was 400 mg. per cent. Death occurred within four months due to chronic pyelonephritis in terminal renal insufficiency. Enuresis was noted in 13 who had previously been "toilet trained," dysuria was noted in 10 and frequency was found in 9 patients. Ten had complained of recurrent flank pain. In each case, flank pain corresponded to the regurgitating side. These children, as a group, were not only normal mentally but seemed to be well adjusted, active and intelligent. Blood pressure elevation was noted in one patient, a 30-year-old woman, with borderline renal insufficiency and pyelographic changes of chronic pyelonephritis.

Associated congenital abnormalities were not common. One patient exhibited imperforate anus and tracheo-esophageal fistula, while another demonstrated ectopic ureter, but reflux did not occur on that side. One boy, aged 4, was found to have interventricular septal defect. Characteristic of this group was prompt response of the toxemia of urinary infection to antibacterial drugs. This was in contrast to those children having frank infravesical obstruction unrelieved. As would be expected, anemia was found only in that patient in advanced renal insufficiency. Two patients demonstrated elevated blood urea nitrogen, one 16 years old, and the other 30 years of age. Residual urine was found to be insignificant in all but one patient who proved to have rapid emptying of regurgitated medium into the bladder, casting doubt on the authenticity of this finding. Polyuria and polydipsia were not noted in any of our patients.

CYSTOSCOPY

Each patient was subjected to cystoscopic examination. In each, the urethra was thought to be normal. Particularly, the bladder neck was thought to be non-obstructive with one exception, a young man who later was found to have no obstruction at open surgical exploration. Careful scrutiny of the bladder wall for trabeculation at low pressures, as well as moderate pressures was carried out. In no case was prominence of the detrusor muscle noted as a definite finding. Twenty-four of the 30 patients were thought to have bladder capacities larger than normal at physiologic pressures. In two, the size of the bladder was not mentioned at cystoscopy and in four the bladder was definitely thought to be of normal size. Patulous ureteral orifice was an evanescent finding in direct proportion to the pressure within the bladder at the time of observation in some. In others, gaping was noted with minimal pressure. It was found that in several patients patulousness did not necessarily lead to reflux and on the other hand apparently normal orifices might reflux even at low pressures (table 2). Therefore, it was felt that this finding was not necessarily a conclusive indication of vesicoureteral regurgitation, though it was strongly suggestive.

PYELOGRAPHY

Twenty-six of the 30 patients had intravenous urograms prior to management. The remaining four had retrograde studies. All but 6 patients had discernible abnormalities of the upper tracts, though in some only to a slight degree. Dilatation of the ureter and pelvis, blunting of the calyces and pyelonephritic contraction of renal parenchyma were characteristic of a few. The majority demonstrated only moderate degrees of uretero-

TABLE 2. *Relationship between rippling, patulous orifice and reflux*

Patient	Patulous Orifice		Reflux		Ripple Sign (I.V.P.)	
	R	L	R	L	R	L
1. V. P.	0	+	+	+	+	0
2. L. T.	0	0	+	+	0	0
3. C. G.	0	+	+	+	0	0
4. L. D.	0	+	0	+	Retrograde	
5. P. W.	0	0	+	0	0	0
6. D. V.	0	0	+	0	+	0
7. D. C.	0	+	0	+	Retrograde	
8. D. M.	+	+	+	+	0	0
9. C. T.	0	0	0	+	0	0
10. T. M.	+	+	+	+	0	0
11. L. L.	+	+	+	+	0	0
12. D. B.	+	0	0	+	0	0
13. S. B.	+	+	+	+	0	0
14. P. H.	0	0	0	+	0	0
15. D. S.	+	+	+	+	+	+
16. S. Y.	+	+	+	+	+	0
17. K. E.	+	+	+	+	+	+
18. C. C.	0	+	+	+	+	0
19. J. S.	0	0	+	+	Retrograde	
20. D. G.	+	0	+	0	0	0
21. J. J.	0	0	+	+	+	+
22. S. V.	0	0	0	+	Retrograde	
23. L. E.	0	0	+	+	0	+
24. J. H.	+	+	0	+	0	0
25. L. M.	0	0	+	+	0	0
26. K. S.	+	+	+	0	+	0
27. M. F.	+	+	+	+	+	0
28. S. N.	0	0	0	+	0	+
29. N. S.	0	+	0	+	0	0
30. B. M.	+	0	+	0	+	0

pyelectasis. Of particular value was the so-called ripple sign (fig. 1). Rippling of the ureter is defined as segmental ureterectasis. This finding was particularly significant in pointing out regurgitation ultimately to be found with cystography. Of the 30 patients believed to have non-obstructive ureteral regurgitation, nine had rippling on one side and three bilaterally (table 2). Where excretory urography was done over a period of years in many cases obvious progression of upper urinary tract damage could be detected when ureteral regurgitation was present and went untreated. Of 13 children followed for a significant period of time on conservative management, nine have shown deterioration of the upper tracts by excretory urography.

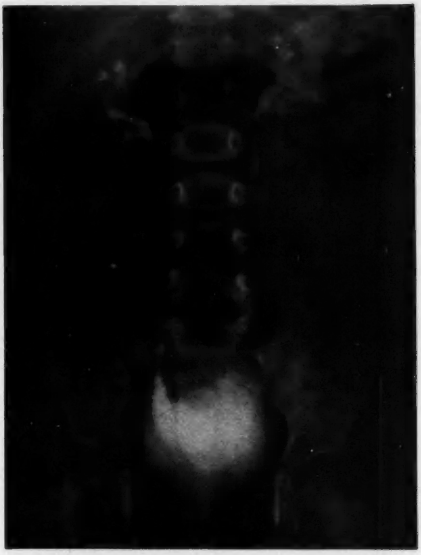


FIG. 1. S. Y. Excretory urogram. Ripple sign on right. Note segmental ureterectasis particularly in lower ureteral segment.

TABLE 3. *Cine-cystourethrography technique*

1. Medium, 20% urokon
2. Instillation per catheter
3. Pressure 20–25 cm. H_2O
4. Fluoroscope at intervals for reflux
5. Fill to urgency
6. Stand to void
7. Film voiding sequences in oblique
8. Assess upper tracts for reflux and vigor of peristalsis

CINE-CYSTOURETHROGRAPHY

Voiding cine-cystourethrography was used at least once in each of these patients to determine not only the tendency to regurgitate, but also to visualize the dynamics of ureteral peristalsis, the pattern of the upper tract when under regurgitation pressure, the size of the bladder, the contour of the vesical orifice during voiding and the degree of emptying under this technique (table 3). The bladder was filled in increments at the end of each of which cine visualization of the upper tracts was made, thereby to estimate pressure necessary to produce regurgitation. Ultimate filling of the bladder was carried out at 20–30 cm. of water pressure. Cine film strips were taken at

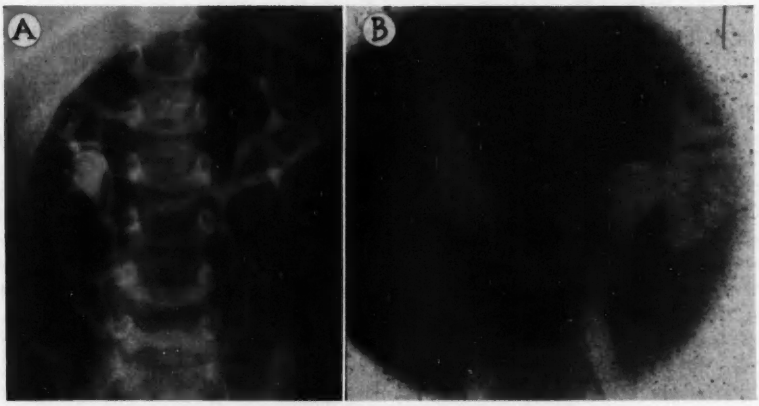


FIG. 2. C. C. *A*, normal excretory urogram. *B*, Cine sequence during regurgitation. Note marked ureterectasis and pyelectasis in comparison to *A*. Enlarged from frame in cine strip.

the voiding phase and during the ureteral emptying phases. The voiding phase was filmed in the oblique projection. Regurgitation unsuspected at cystoscopic examination was not uncommonly observed at cine-cystourethrography. Careful evaluation of ureteral peristaltic vigor carried with it significant prognostic value in predicting the patient's response to an anti-reflux surgical procedure. We came to be aware of what properly should be referred to as incompetent peristalsis, in which a peristaltic wave progressing downward might at the same time propel urographic medium upward when the trailing segment of the ureter following the bolus of urine did not completely and tightly close. Cephalad leakage was thus allowed. Regurgitation at low pressure was often accompanied by more drastic changes in the upper tract. Bladder filling was carried out in the supine position while voiding took place standing, age permitting. Inducing a child to void was surprisingly easy when fear had been eliminated. The greatest success was obtained in children hospitalized and in no contact with their parents.

CYSTOMETRY

Of the 30 patients included in this category, cystometrographic voiding pressure studies were performed in 13. These studies were carried out on an Electronics for Medicine polygraph employing a Statham transducer. In the smaller children the suprapubic puncture technique was used, and in the older children size 4 ureteral catheters were passed per urethram. The values obtained by this method of polygraphic recording are materially higher than those obtained by any one of several conventional cystometers. This disparity is because of the fact that the reductions in values secondary to fluid inertia, volume displacement and viscosity of the solutions are eliminated. While average voiding pressure in normal children was found to be 135 cm. water, frank bladder neck contractures and obstructions were found to yield an average of 244 cm. water pressure on voiding. Patients with nonobstructive vesicoureteral regurgitation were found to have voiding pressures identical with those of normal patients, with no overlapping of pressures with bladder neck obstruction.

DISCUSSION

From these studies there seems to be reasonable evidence that vesicoureteral regurgitation can and does occur in the absence of infravesical obstruction. Cine-sequences of voiding cystograms show no evidence of contracture at any point along the urethral channel in these patients. While not all of our patients have been evaluated as to voiding pressures, none in this group displayed abnormally high voiding pressure. Further, these children had none of the vesical stigmata of obstruction, viz. trabeculation or muscular hypertrophy. While this essay does not include in its scope the management of this disorder, 11 children have been subjected to anti-regurgitation operations, and in each, careful inspection of the bladder wall showed no thickening or trabeculation, and in eight the bladder

wall was remarkably thin. This is in sharp contrast to those findings in frankly obstructed bladders where detrusor hypertrophy is the rule. While one might argue that a thin bladder wall might be a late sequela of obstruction, one should find large volumes of residual urine, diverticula, cellules, severely damaged upper tracts and intense unremitting infection. This has not been the case. On the contrary, damage is minimal in the young children, progress of upper tract damage has been slow and in some cases, controllable with conservative measures.

Edwards,[5] Beeson,[6] and Bumpus[7] have noted that a significant number of patients with chronic pyelonephritis display reflux. An attractive explanation for this observation is to attribute reflux to secondary fibrotic inflammatory changes in the ureterovesical segment rendering it rigid and incompetent. On the other hand, we submit that regurgitation itself may precede, promote, and perpetuate pyelonephritis. The frequent observation of large, thin bladder in these children suggests that the intramural ureteral segment is short, and may be an explanation for the whole train of events and changes. Mega-trigone, as observed by Paquin and Marshall[1] is probably only a reflection of the large, thin bladder.

The advantages of cineradiographic investigation in these children are quite evident. A higher yield of observable reflux can be expected. The dynamics of both upper and lower urinary tracts are simultaneously evident. Absence of vesical neck obstruction on voiding cine sequences is considered an integral part of the diagnosis in this disorder.

Finally, the prolonged history of recurrent or resistant urinary infection, especially in little girls, together with the observation of the ureteral ripple sign at excretory urography should strongly suggest this syndrome and make appropriate diagnostic measures mandatory.

SUMMARY AND CONCLUSIONS

Pertinent clinical diagnostic findings in 30 patients with vesicoureteral regurgitation are presented. The conclusion that regurgitation is not precipitated by infravesical obstruction or neurologic disease in these people seems justified. The advantages of cineradiographic diagnosis are cited. Attention is called to the so-called ureteral ripple sign, which suggests regurgitation. The etiology of regurgitation in this syndrome seems related to a primary thinness of bladder wall and consequent shortening of the intramural ureteral segment. No attempt in this essay is made to establish therapeutic criteria or methods.

The authors acknowledge with gratitude the cineradiographic assistance of Drs. J. A. Campbell and Eugene Klatte and the inclusion of cases of Drs. R. D. Howell, William Walton and Joseph McKinley.

[5] Edwards, David: Cineradiology in congenital bladder neck obstruction and mega-ureter. Brit. J. Urol., **29:** 410–415, 1957.

[6] Beeson, Paul: Factors in the pathogenesis of pyelonephritis. Yale J. Biol. & Med., **28:** 81–87, 1955.

[7] Bumpus, H.: Urinary reflux. J. Urol., **12:** 341–6, 1924.

ATROPHIC PYELONEPHRITIS FROM URETERAL REFLUX WITHOUT OBSTRUCTIVE SIGNS ("REFLUX PYELONEPHRITIS")

FRANK HINMAN, JR. AND JOHN A. HUTCH

From the Division of Urology, University of California School of Medicine, San Francisco 22, Cal.

We had always considered the end-point of vesicoureteral reflux to be hydroureter and hydronephrosis until, while making cineradiographic studies, we discovered a patient who clinically and radiologically appeared to have chronic *non-obstructive* pyelonephritis but who actually had bilateral ureteral reflux. This finding was unexpected, since ureteral dilatation or hydronephrosis was not present during excretory urography, and led us to suspect that other patients being treated medically for chronic pyelonephritis basically may have a urologic disorder. A cineradiographic search has disclosed eight more cases.

It has been usual to place patients with chronic pyelonephritis into one of two large groups: those with hematogenous or para-ureteral lymphatic origin (*chronic non-obstructive pyelonephritis*), and those in whom lower tract obstruction produced alterations in the detrusor and ureterovesical valve, allowing reflux and the development of hydroureter and hydronephrosis (*obstructive pyelonephritis*).

The traditional key diagnostic test to separate the non-urologic from the obstructive urologic groups has been the excretory urogram. If the urogram revealed no dilatation of the ureter or renal pelvis, the disease was called idiopathic or non-obstructive pyelonephritis. The existence of reflux in patients with urograms showing an obstructed and dilated urinary tract has long been recognized. But reflux has not been suspected in patients with non-obstructive pyelonephritis and the renal infection has been thought to be usually hematogenous in origin.

We are then concerned here with patients who appear to be in an intermediate stage between the non-obstructive and obstructive groups (table 1). How far they will encroach upon the non-obstructive group, only further observation will tell.

Supported by the Breon Fund of the University of California School of Medicine and U.S.P.H.S. Grant CS9440 to Dr. Earl R. Miller, Radiological Research Laboratory, University of California School of Medicine, San Francisco 22, California.

The clinical picture of chronic non-obstructive pyelonephritis is well known. Many patients remain asymptomatic except for occasional flare-ups of acute pyelonephritis. In later stages, uremia and hypertension supervene. Constant or intermittent albuminuria and bacilluria are often present, as are varying degrees of pyuria. X-ray studies reveal calyceal blunting and areas of thinning in the cortex, and often a very atrophic kidney. Rarely does any patient reveal all of these features at one time. A diagnosis of chronic, non-obstructive pyelonephritis would have been made in each of the patients presented on the basis of the history, physical examination, laboratory studies and the intravenous urogram.

CLINICAL MATERIAL (TABLE 2)

Nine patients have been studied. Six were young women; one was a woman 58 years of age and two were males. A majority had had symptoms for a relatively short time; only 3 patients had had symptoms dating back to childhood. In 5 patients, the left kidney, and in three, the right kidney was atrophic. In one, the right kidney was smaller but not truly atrophic. Reflux was bilateral in six of the 9 cases; in the other three it occurred only on the side of the renal atrophy. Evidence of concomitant obstruction of the ureterovesical junction was present bilaterally in only 1 case and was seen to a lesser degree in a second.

Five patients gave no evidence of vesical neck obstruction, having neither residual urine nor vesical trabeculation. Three patients had residual urine greater than 30 cc and one had a urethral valve demonstrable on voiding cystography. Total renal function by the phenosulfonphthalein (PSP) test was normal in all but 2 patients. Hypertension was present in three of the 9 patients.

The first case, the patient which led us to suspect the presence of a syndrome, may be considered as the prototype, since obstructive symptoms were absent and the reflux was wholly unexpected.

Case 1. A 16-year-old girl (referred by Dr. Sam

Peck of San Diego) had been in good health except for occasional headaches. One year ago, on routine examination her blood pressure was found to be 220/110 mm. Hg. and the urine was infected with E. coli. PSP excretion was 40 per cent in 1 hour; residual urine measured by catheterization varied between 5 cc and 60 cc, and intravenous urograms failed to show excretion on the left. Differential function was 3 per cent PSP excretion in 30 minutes on the left, 16 per cent on the right, and retrograde pyelograms showed left renal atrophy (fig. 1, *A*). A cystogram done before her study here showed no ureteral reflux (fig. 1, *B*).

Cinefluorography showed bilateral reflux without ureteral dilatation (fig. 1, *C*). She was able to empty the bladder completely. The residual urine which had been previously noted was due to efflux from the ureters after voiding.

TABLE 1

CHRONIC NON-OBSTRUCTIVE PYELONEPHRITIS
↓
REFLUX PYELONEPHRITIS
↓
INFECTED HYDRONEPHROSIS AND HYDROURETER

TABLE 2. *Clinical data*

Case No. and Sex	Age	Age at First Symptoms (Yrs.)	Atrophic Kidney, Side	Reflux		Ureterovesical Junction Obstruction		Vesical Neck Obstruction	Total Function (1 hr. PSP) per cent	Blood Pressure mm/Hg.	Treatment
				Right	Left	Right	Left				
1 (F)	16	15	L	+	+	0	0	0	40	220/110	Ureteral dilation
2 (F)	28	childhood, then free	L	+	+	0	0	0	37	140/100	Supportive
3 (M)	33	19	R, then left	+	0	0	0	30 cc residual urine	10	210/160	Supportive
4 (F)	58	no symptoms	R	+	0	0	0	vesical trabeculation	50	normal	Right nephroureterectomy
5 (F)	15	3	L	±	+	±	±	90 cc residual urine	70	normal	Left nephrectomy, left ureterectomy
6 (F)	21	birth	L	+	+	±	±	60 cc residual urine	60	normal	Right ureteroneocystostomy
7 (F)	27	20	R	+	0	0	0	0		normal	Supportive
8 (M)	13	10	L	0	+	0	+	urethral valves	65	normal	Left ureteronephrectomy and excision of valves
9 (F)	34	26	R	+	+	0	0	0	70	normal	Essentially asymptomatic

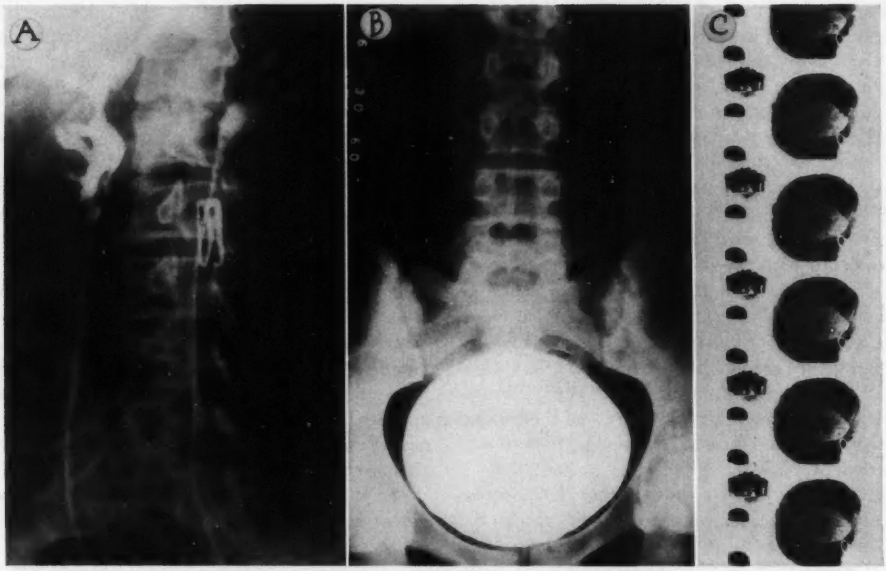


FIG. 1. Case 1. *A*, retrograde pyelogram (excretory urogram was similar but could not be as well reproduced photographically) shows left atrophic pyelonephritis, with pyelonephritic changes on right, but without pelvic or ureteral dilatation. Film would be interpreted as showing chronic, non-obstructive pyelonephritis. *B*, routine cystogram. No reflux. *C*, voiding cinefluorograph shows bilateral reflux.

Treatment consisted of antibiotic therapy, urethral dilatation, and an anti-hypertensive regimen. Her blood pressure is now 170/90. mm. Hg. and her urine remains infected.

The subsequent cases illustrate the varying aspects of the disorder.

Case 2. A 28-year-old woman had had urinary tract infections as a child, but the attacks disappeared during adolescence. During her second pregnancy in 1958, hypertension and albuminuria developed without bacteriuria; these findings have persisted to date.

Excretory urograms (fig. 2) were interpreted as showing normal pelves and calyces, but cystoscopy revealed gaping orifices. The ureters appeared to run vertically rather than obliquely through the vesical wall. Retrograde pyelograms outlined a small left kidney with a thin parenchyma. Her blood pressure was 140/100 mm. Hg. and the PSP excretion was 37 per cent in 1 hour. Cystography and cinefluorography showed bilateral reflux, and filled out a dilated ureter and small pelvis on the left side, and a dilated ureter and pelvis on the (better) right side. These obstructive changes were not seen on the excretory films.

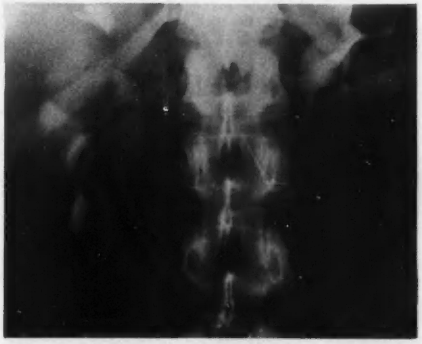


FIG. 2. Case 2. Excretory urogram shows left renal atrophy and right chronic pyelonephritis. Pelvic and ureteral dilatation is absent, yet cinefluorography showed bilateral reflux with bilateral ureteral dilatation.

Case 3. A 33-year-old man was first noted to have albuminuria at the age of 19. Investigation 3 years later because of the albuminuria revealed right renal atrophy and compensatory left renal hypertrophy with mild dilatation of the pelvis. The urine was infected with E. coli. The total renal function by PSP test was 52 per cent in 1 hour, but the delayed curve of excretion sug-

gested the presence of residual urine. The blood pressure was normal.

Cystoscopy showed bilaterally dilated ureteral orifices but no vesical trabeculation. A cystogram showed reflux up the right ureter.

Eleven years later, at the age of 33, his blood pressure was 210/160 mm. Hg. Retrograde pyelograms showed bilateral renal atrophy (fig. 3). PSP excretion was 10 per cent in 1 hour and cinefluorography showed immediate right reflux with incomplete emptying of the bladder.

His condition has gradually deteriorated from the effects of progressive renal failure.

Case 4. A 58-year-old woman had excretory urograms in 1952 as part of a routine investigation of lumbosacral back pain. The urograms showed right renal atrophy. She was then found to have infected urine. Her blood pressure was normal.

Cystoscopy in 1961 showed vesical trabeculation and a saccule appeared to lie above the right ureteral orifice. Retrograde pyelograms confirmed the findings of the previous excretory urograms (fig. 4). Cinefluorography showed reflux on the right, past a 2 cm. saccule. After a right nephro-ureterectomy, her course has been uneventful. Pathologic examination showed marked atrophic pyelonephritis (fig. 5).

Case 5. A 14-year-old girl had more stigmata of obstructive pyelonephritis. She had had pyelonephritis at the age of 3 years. When she was 7, she was found to have 90 cc residual urine, a trabeculated bladder and bilaterally dilated ureters. At age 11, her urine was infected but her total renal function was 70 per cent in 1 hour. Her left kidney was then seen to be very small by excretory urography (fig. 6, *A*). Left reflux appeared on cystography (fig. 6, *B*). The left kidney was removed. Sections showed marked atrophy (fig. 7).

She is now 14 and cinefluorography for persistent infection shows reflux up the left ureteral

FIG. 3. Case 3. Retrograde pyelogram. Bilateral chronic pyelonephritic changes without appreciable obstructive changes. Cinefluorography showed immediate reflux on right, with moderate ureteral dilatation.

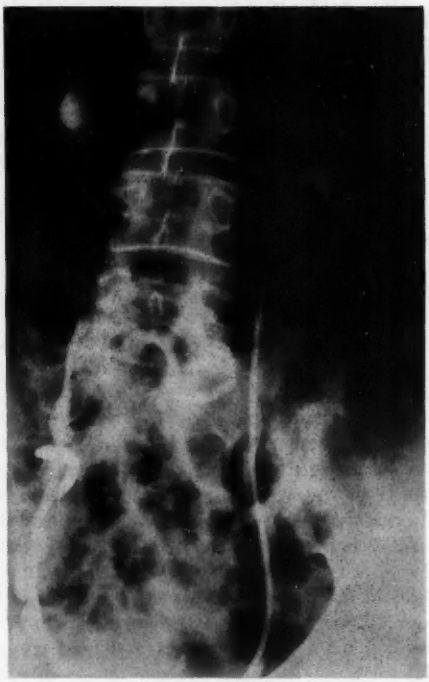


FIG. 4. Case 4. Retrograde pyelograms show right atrophic pyelonephritis without appreciable obstructive changes.

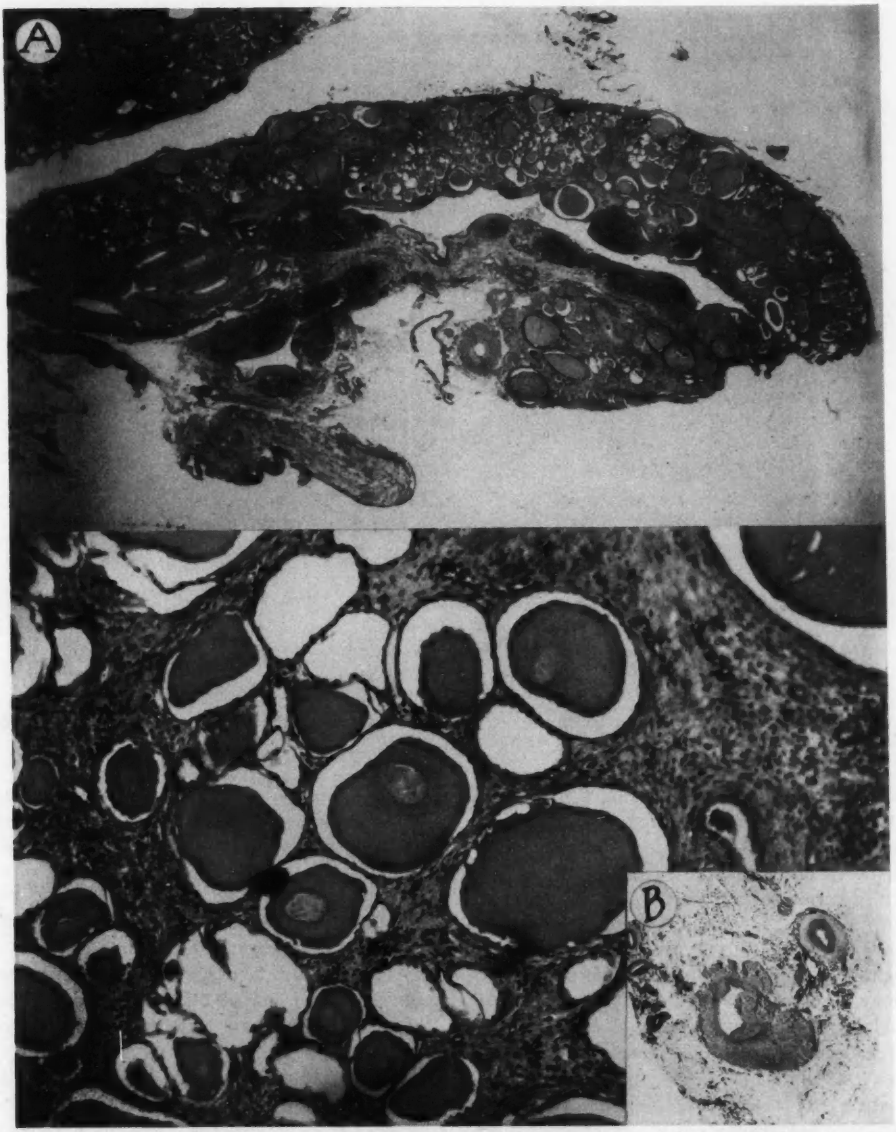


FIG. 5. Case 4. Photomicrograph (×5) of atrophic renal parenchyma and slightly thickened ureter

stump, and up the right ureter as well. Her total renal function has remained good. Recently, the remaining portion of the left ureter was removed, without change in her persistent urinary infection.

Case 6. A 21-year-old woman had had symptoms of lower urinary tract infection since birth. Her urine was infected with E. coli and her total renal function was 60 per cent PSP excretion in 1 hour. In January 1959, she had a right oblique ureteroneocystostomy because of bilateral reflux. The reflux on the right was corrected by the operation.

At present, her urine is infected. The intra-

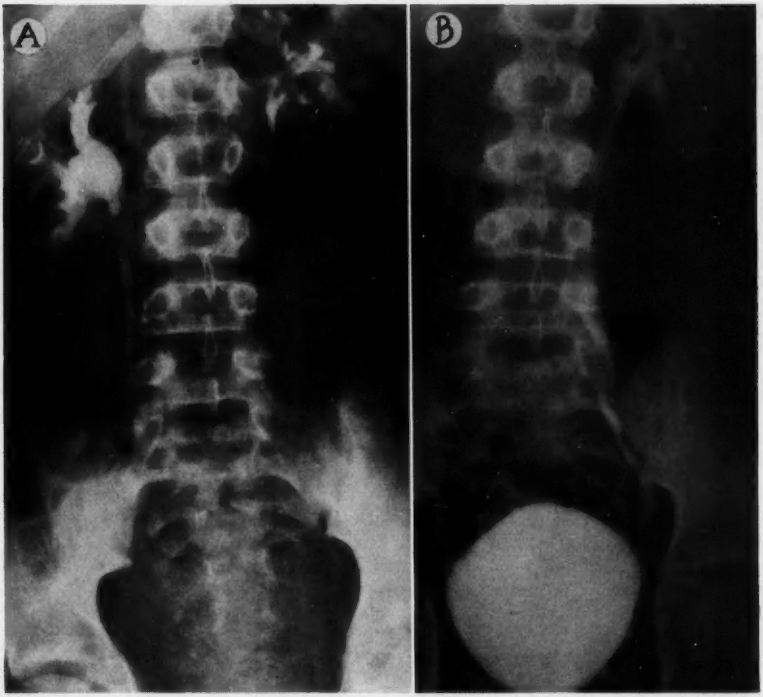


FIG. 6. Case 5. *A*, excretory urogram shows left atrophic pyelonephritis without evidence of obstruction. *B*, cystogram. Left ureteral reflux with ureterectasis.

venous urograms show changes of chronic atrophic pyelonephritis with some dilatation on the left side (fig. 8) with lesser changes on the right. Cinefluorographic study shows left reflux and renal atrophy.

Case 7. A 27-year-old woman had been well until the age of 20 when recurrent cystitis and right pyelonephritis developed. After a hysterectomy in January 1961, she had right renal pain and her temperature rose to 105F. The blood pressure was 122/90 mm. Hg. and residual urine was less than 10 cc.

Intravenous urograms showed right pyelonephritis but no obstruction or ureteral dilatation (fig. 9, *A*). A cystogram was normal during filling (fig. 9, *B*), but on voiding, free reflux occurred up the right ureter (fig. 9, *C*). Cinefluorographic studies confirmed these findings and revealed no residual urine.

Case 8. A 13-year-old boy had had bladder infection for 2 years. His urine was infected with Proteus vulgaris, total renal function was 65 per cent PSP excretion in ½ hour. Excretory urograms and retrograde pyelograms showed a contracted left kidney with some ureteral dilatation (fig. 10, *A*). A saccule was present at the left ureterovesical junction. Cystography showed filling of the saccule and left ureteral reflux (fig. 10, *B*). At cystoscopy the left ureter was seen to empty into the floor of the saccule. Urethral valves were visualized by panendoscopy below the verumontanum and were destroyed by fulguration.

Left nephro-ureterectomy was done, removing an atrophic kidney (fig. 11). His total renal function was unchanged by the operation. Six months after operation he was asymptomatic, but his urine still contained Proteus bacilli.

Case 9. A 34-year-old woman remembered having some urinary symptoms in childhood, but she had no further trouble until 8 years ago when she had three bouts of pyelonephritis during her first pregnancy. Intravenous urograms at that time were normal. One year ago cystitis occurred

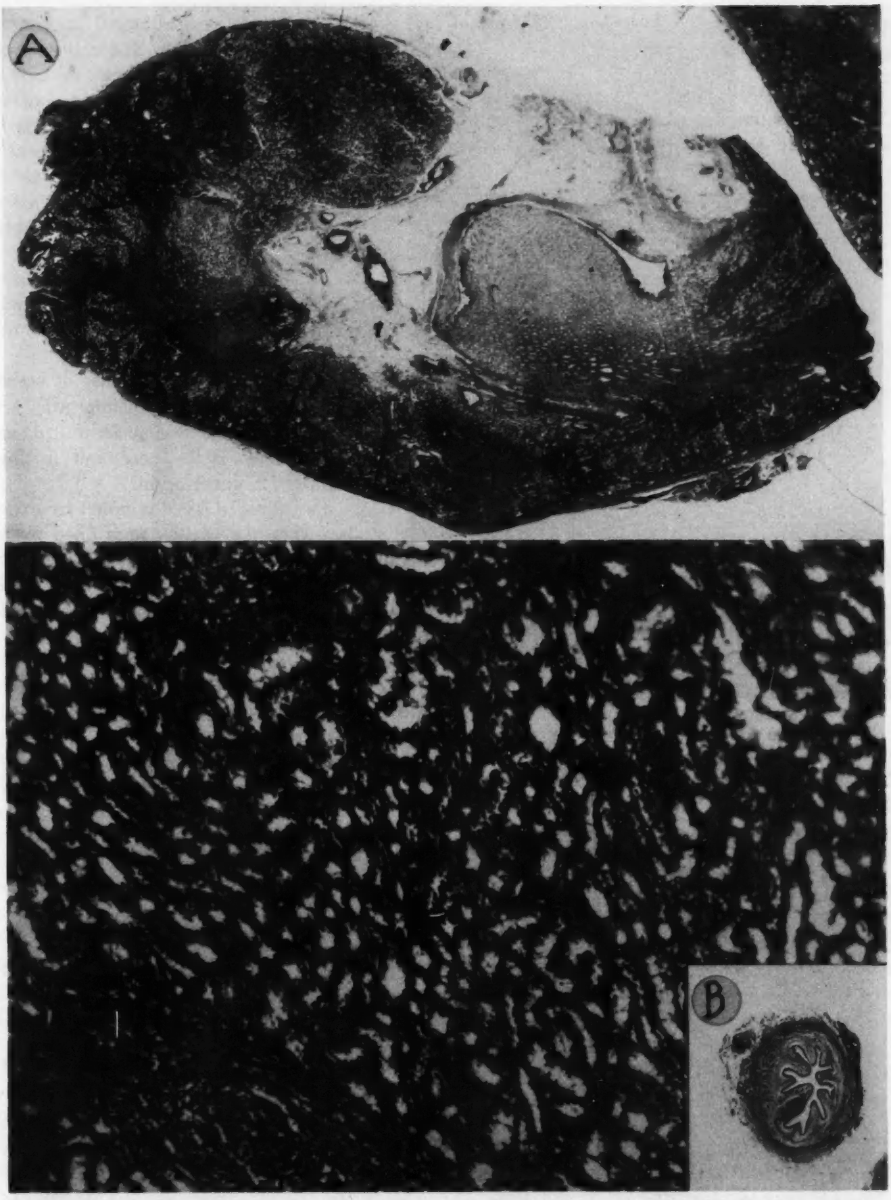


FIG. 7. Case 5. Photomicrograph (×5) shows marked atrophic pyelonephritis. Ureter appears essentially normal.

and her urine has been infected since in spite of therapy. She notices low back pain on urination if she is dehydrated.

Recent intravenous urograms (fig. 12, *B*), when compared with previous urograms (fig. 12, *A*), showed a decrease in size of both kidneys, especially on the right. Cystoscopic examination showed mild vesical trabeculation and large, ob-

lique orifices with thick anterior cusps. Cineradiography showed bilateral reflux.

RADIOLOGIC STUDIES (TABLE 3)

Intravenous urograms, which were done in all cases, usually showed the affected side to be poorly functioning, with a small renal shadow and an irregularly thinned cortex. The calyces were clubbed with narrowed infundibula. A normal distribution of calyces was present, in contrast to the findings in congenital renal hypoplasia. In several cases the affected renal pelvis appeared baggy, but no hydronephrotic dilatation was observed. The upper ureter was usually normal in caliber. The lower ureter was occasionally slightly dilated.

FIG. 8. Case 6. Detail of excretory urogram shows left renal atrophy without obstructive changes.

Two patients had saccules at one ureterovesical junction. In one case, the bladder was otherwise normal (case 4) and in the other, the saccule was associated with urethral valves.

In three other cases, some evidence of vesical abnormality was present. One bladder was trabeculated and another was smooth-walled and larger than normal. Both these and a third bladder contained residual urine.

Despite the lack of dilatation noted by excretory studies when the ureters were filled by reflux during cineradiography, they were seen to be unusually distensible, especially in the lower third. Frequently the whole upper tract would balloon out as the urine from the bladder refluxed up the ureters during voiding. Reflux often would begin during filling, but would be most complete during micturition. At the end of urination the bladder would be empty, only to slowly refill from the dilated ureter.

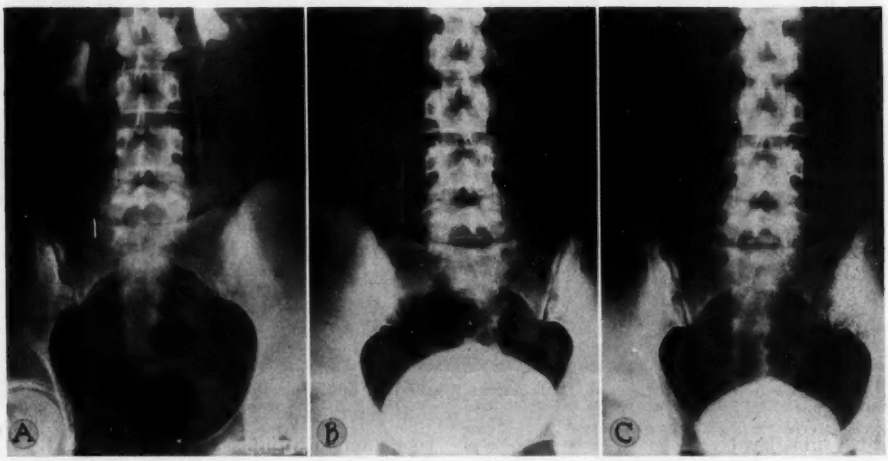


FIG. 9. Case 7. *A*, excretory urogram shows right pyelonephritis without obstructive changes. *B*, cystogram during filling. No reflux. *C*, voiding cystogram shows reflux up right lower ureter.

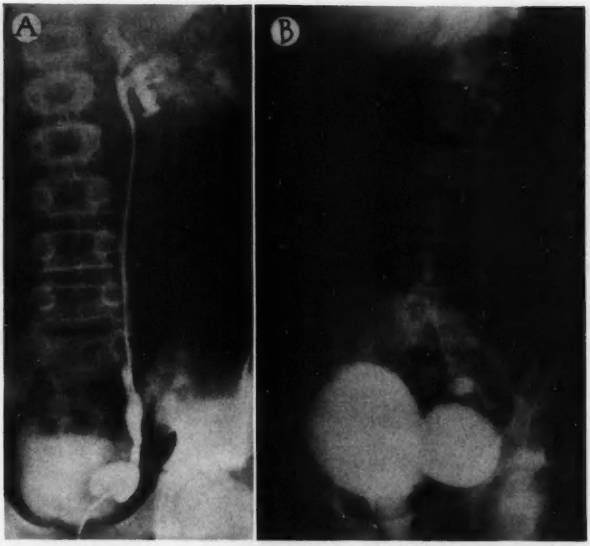


FIG. 10. Case 8. *A*, left retrograde pyelogram shows atrophic pyelonephritis without pyelectasis. Saccule is partially filled. *B*, cystogram. Saccule and lower ureter filled.

PATHOLOGIC STUDIES (TABLE 4)

The 3 kidneys which were removed were very small, averaging 30 gm. in weight. Gross examination in all cases revealed an irregular cortical surface with a thickened capsule which usually was difficult to strip off. The thickness of the pelvic and calyceal walls was also increased.

Microscopic examination (figs. 5, 6, *B* and 10, *B*) showed cortical clusters of fibrotic, hyalinized glomeruli. Bowman's capsule was thickened, yet an occasional Malpighian tuft was intact. Many of the tubules contained "colloid" casts. Interstitial fibrosis was widespread and often patchy, as would be expected from the repeated episodes of infection. In one kidney (case 4), there were several foci of virtually normal renal substance. The arterioles were frequently seen to be involved in endarteritis obliterans. These changes were indistinguishable from those in non-reflux pyelonephritis. The renal pelves and calyces had marked thickening of the lamina propria, with characteristic focal and diffuse infiltration with lymphocytes.

The ureters, in contrast, showed only moderate thickening of the mucosa and submucosa, and an increase in the muscular coat. Evidence of chronic inflammation (lymphocytic infiltration) was occasionally present.

OBSERVATIONS OF OTHERS

While studying reflux in children, McGovern, Marshall and Paquin[1, 2] presented 3 cases similar to ours. Hodson and Edwards[3] studied 20 patients with chronic pyelonephritis, and found eight who were in the teens or older who showed reflux by cystography.

DISCUSSION

Disorders of the ureterovesical valve usually produce both reflux and ureteral obstruction, but we now appreciate that they may produce either one without the other. Obstruction alone is seen in the child with a dilated ureter with an aperistaltic, unsupported termination at the bladder, yet without reflux. The present dis-

[1] McGovern, J. H., Marshall, V. F. and Paquin, A. J., Jr.: Vesicoureteral regurgitation in children. J. Urol., **83:** 122, 1960.

[2] Paquin, A. J., Jr., Marshall, V. F. and McGovern, J. H.: The megacystis syndrome. J. Urol., **83:** 634, 1960.

[3] Hodson, C. J. and Edwards, D.: Chronic pyelonephritis and vesicoureteric reflux. Clin. Radiol., **11:** 219, 1960.

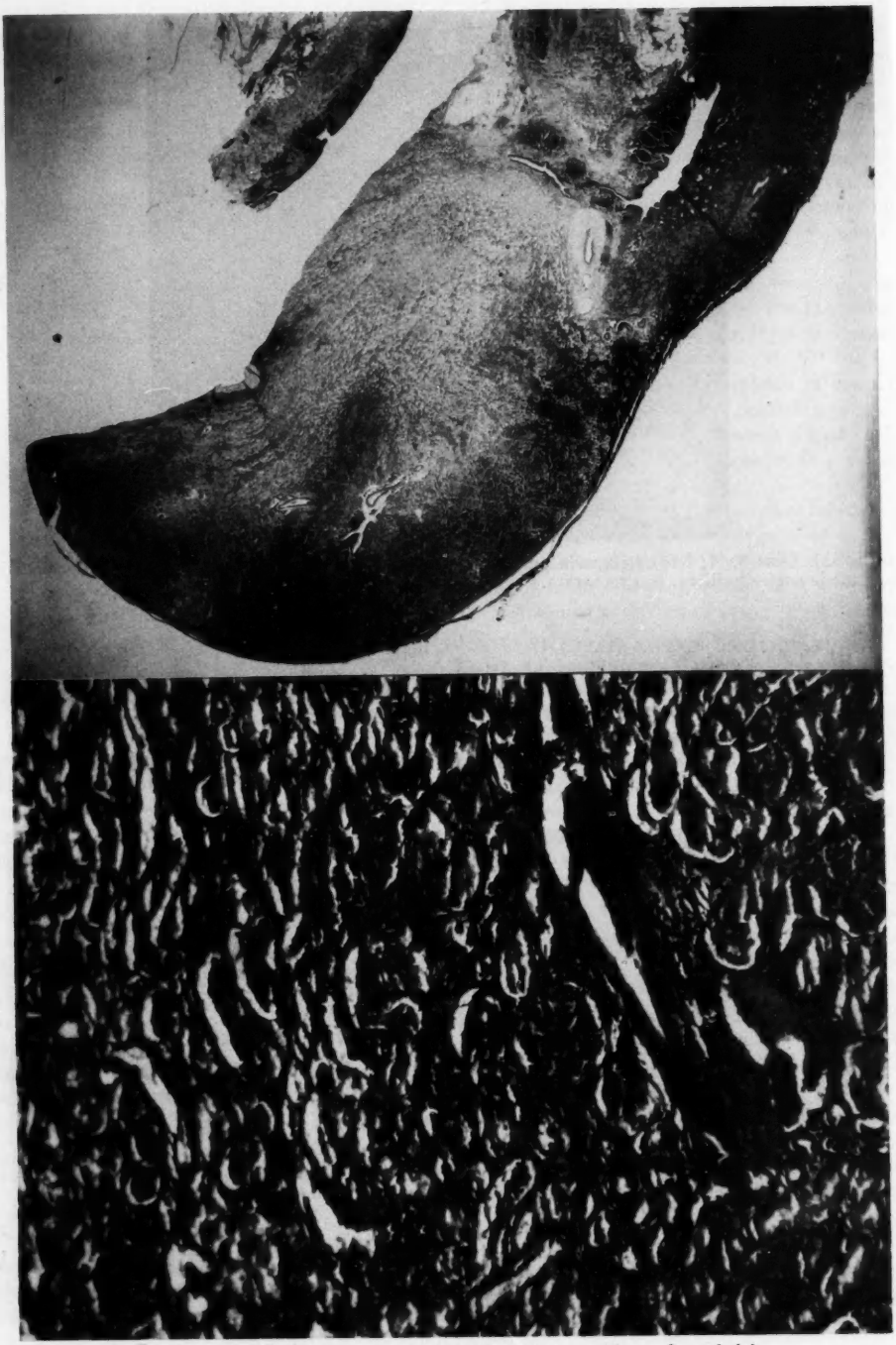


FIG. 11. Case 8. Photomicrograph (×5). Left atrophic pyelonephritis

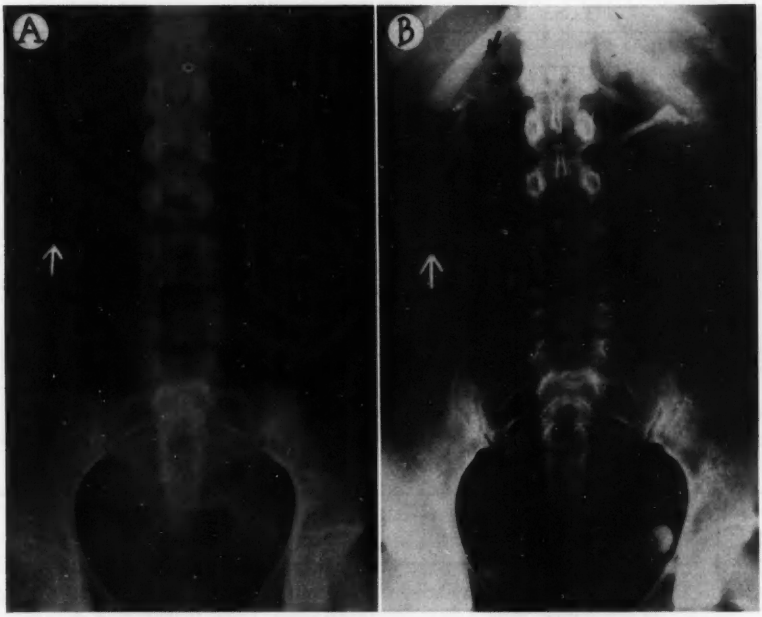


FIG. 12. Case 9. *A*, excretory urogram, 1955, shows essentially normal upper tracts. *B*, excretory urogram, 1961, shows decrease in size of right kidney.

cussion, in contrast, is concerned with the effects of a ureterovesical junction which permits regurgitation of urine and yet does not hinder its free outflow.

Whether the cause of the disorder of the ureterovesical valve is primary, due to congenital abnormality of the bladder, or is secondary, due to alterations from chronic infection, remains uncertain. Williams[4] showed that reflux may cease in certain cases when the infection is cured. Thompson[5] observed reflux in 14 patients studied by cineradiography during an attack of acute cystitis; none had reflux when restudied after cure of the infection. Hanley[6] has made similar observations. However, the association of saccules in two of our cases and the presence of residual urine and other evidence of vesical abnormality in three others suggests that abnormal formation of the vesical apparatus may be the more important etiologic factor in the cases under discussion. In other words, it is probable that we are seeing in the adult patient the later stages of a childhood disorder (loosely conceived of as the megacystis-megaureter complex). That the disorder often becomes manifest earlier is shown by Kjellberg and associates[7] who found 18 atrophic kidneys among 99 children with reflux and urinary infection, and one might assume that in the cases under discussion the anatomic abnormalities were present early but were not severe enough to become evident during childhood.

Reflux without obstruction may damage the kidney either by backpressure or by repeated conveyance of bacteria to the kidney. Many animals normally have reflux which does not produce renal damage unless infection is introduced. So backpressure would not appear to be the sole cause, but even temporary ureteral obstruction so changes the tissue defenses that infection is established in the kidney,[8] just as experimental obstruction of the bladder neck will visibly alter the vesical mucosa and prevent it from eradicat-

[4] Williams, D. I.: Megacystitis and megaureter in children. Bull. N. Y. Acad. Med., **35:** 317, 1959.
[5] Thompson, I.: Personal communication.
[6] Hanley, H.: Personal communication.
[7] Kjellberg, S. R., Ericsson, N. O. and Rudhe, U.: The Lower Urinary Tract in Childhood. Chicago: The Year Book Publishers, Inc., 1957.
[8] Gorrill, R. H.: Bacteriology and pathogenesis of experimental pyelonephritis. In: Biology of Pyelonephritis, ed. by Quinn, E. L. and Kass, E. H. Boston: Little, Brown and Co., 1960.

TABLE 3. *Radiologic data from excretory urogram*

Case No.	Side	Reflux	Cortex	Calyces	Pelvis	Upper Ureter	Lower Ureter	Saccule (From Cystogram)	Bladder (From Cystogram)
1	R	+	N	N	N	N	N	0	N
	L	+	↓	spidery	N	N	N	0	
2	R	+	N	narrowed	large	N	large	0	N
	L	+	↓	short	N	N	N	0	
3	R	+	↓	narrowed	baggy	N	slightly dilated	0	N
	L	0	↓	narrowed	N	N	N	0	
4	R	+	↓	short, contracted	large	slightly redundant	slightly dilated	+	N
	L	0	N	slightly elongated	N	N	N	0	
5	R	±	N	N	N	N	N	0	large
	L	+	↓	spidery	N	large	large	0	
6	R	+	N	narrow	N	N	slightly dilated	0	N
	L	+	↓	narrow	N	N	dilated	0	
7	R	+	slight ↓	elongated	N	N	N	0	N
	L	0	N	irregular	N	N	N	0	
8	R	0	N	N	N	N	N	0	large
	L	+	↓	narrow	N	N	dilated	+	
9	R	+	↓	N	N	N	N	0	N
	L	+	N	N	N	N	N	0	

N = normal or not remarkable 0 = absent
+ = present ↓ = decreased

TABLE 4. *Pathologic data*

Case	Renal Weight and Size	Cortical Thickness	Pelvis	Ureter
Case 4	17 gm., 5.5 × 2.5 × 2 cm.	0.5 cm.	thickened	essentially normal size, chronic inflammation
Case 5	41 gm., 6.5 × 3.5 × 2.7 cm.	0.6 cm.	thickened	slightly increased thickness
Case 8	32 gm., 6 × 3 × 2 cm.	0.6 cm.	thickened	increased thickness

ing bacteria.[9] Vivaldi and co-workers,[10] in studies on rats, which normally reflux, obtained pyelonephritis in 75 per cent of cases merely by insertion of a foreign body in the bladder along with

[9] Mehrotra, R. M. L.: An experimental study of the vesical circulation during distension and in cystitis. J. Path. Bact., **66:** 79, 1953.

[10] Vavaldi, E., Cotran, R., Zangwill, D. P. and Kass, E. H.: Ascending infection as a mechanism in pathogenesis of experimental non-obstructive pyelonephritis. Proc. Soc. Exper. Biol. and Med., **102:** 242, 1959.

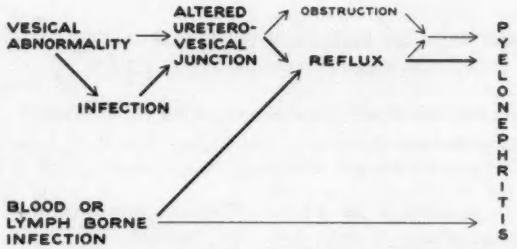


FIG. 13. Diagram of relation between non-obstructive reflux and obstructive pyelonephritis. Heavy lines show routes concerned in cases under discussion.

bacteria. Persistent vesical infection in the presence of reflux promoted the establishment of renal infection.

An analogous state is chronic pyelonephritis seen after ureterosigmoidostomy. Ureteral and pelvic dilatation may be minimal, but widespread damage is found in the kidney from the recurrent reflux and infection.

Chronic infection appears to be a necessary adjunct to reflux if progressive destruction of the kidney is to occur (fig. 13). Both infection and reflux were found in the cases which have been presented.

SUMMARY AND CONCLUSIONS

Although chronic, non-obstructive pyelonephritis is generally considered to be hematogenous in origin rather than due to ascending urinary tract infection, 9 cases are presented in which vesicoureteral reflux was demonstrable.

The characteristics of "reflux pyelonephritis," based on these observations in young adults, typically without a history of long-standing urinary tract infection, are: absence of obstructive changes by excretory urography, the presence of renal atrophy, and the occurrence of vesicoureteral reflux.

The course of the disorder may be one of progressive renal destruction, since the patient is usually seen after irreversible inflammatory changes have occurred.

Patients, especially young women, who clinically and radiologically appear to have chronic non-obstructive pyelonephritis, deserve routine cystography, preferably with fluoroscopic monitoring, to detect unsuspected reflux.

The work would not have been possible without the constant aid of Dr. Earl R. Miller, professor of radiology, not only in providing incomparable facilities but day by day assistance and advice.

THE IMPORTANCE OF URETHRAL VALVES AS A CAUSE OF VESICAL NECK OBSTRUCTION IN CHILDREN

KEITH WATERHOUSE AND FRANK C. HAMM

From the Department of Surgery, University of the State of New York, Downstate Medical Center, Brooklyn 3, N. Y., and the Division of Urology, Kings County Hospital, Brooklyn, N. Y.

Observations currently reported in the American literature concerning urinary bladder dysfunction in infancy and childhood have made scant reference to the valvular type of obstruction occurring in the posterior urethra. The prevailing opinion is that this type of obstructive lesion is exceedingly rare. In a panel discussion conducted at the New York Academy of Medicine in February, 1961,[1] there were few references to the valve as an important factor in obstruction. Leadbetter[2] has recently published his experiences, reporting 35 children with bladder neck obstruction. He mentions the diagnosis of a valvular lesion in only one patient, the diagnosis having been made before the child was placed in his care. Burns[3] described in 1955 a large series of 81 children with obstruction. Only three were diagnosed as valves, 78 having been classified as bladder neck obstructions. (In his discussion of this paper, Dr. Burns indicated that he had since discovered 6 valves.) On the other hand, Herbut[4] in his textbook on Pathology of the Urinary Tract, states, "This is the second most common of all congenital lesions of the urethra, being exceeded only by stenosis of the external meatus." Twenty-two instances of the urethral valve were reported by Nesbit, Thirlby and Raper[5] in 1951, and a similar series by Gross.[6] Campbell[7] reported 63 instances of valves. Williams,[8] the English surgeon, stated, "Valvular formation of mucosal folds in the posterior urethra is the most often encountered example of the group of congenital anomalies which cause urethral obstruction." The Swedish authors, Kjellberg and associates[9] reported it as a frequent finding. Since 1958 we have discovered 16 patients with posterior urethral valves; 15 have undergone operation. Until 1919, valve formations were known almost exclusively to the pathologist. At that time Young[10] reported his observations on their presence. He also submitted a classification which has been the basis of most discussions since that time.

What are valves? They are defined as folds in the posterior urethra which cause urinary obstruction. When studied in microscopic section they are composed of two layers of epithelium and a small amount of stroma. Between the layers is an occasional strand of smooth or striated muscle. The disorder is, for practical purposes, confined to the male. Although the exact cause of the formation of urethral valves is not known, a likely explanation could be a persistence of the temporary folds normally occurring in the region of the verumontanum. They arise from the wall of the urethra and protrude into its lumen and are usually attached at one end to the verumontanum. Rarely the valves are found to be partial or complete diaphragms and show a wide range in location and conformation. In the more usual leaflet type of valve, as the fluid stream from the bladder strikes the mucosal folds the valve balloons into cusp formation, resembling in action the heart valves. They are to be distinguished from the low ridges which are merely exaggerations of the normal frenulae of

This work was supported, in part, by a grant from the Michael Melamed Fund for Pediatric Urological Research.

[1] Meeting of the Section on Urology, New York Academy of Medicine, February 1961.

[2] Leadbetter, G. W., Jr. and Leadbetter, W. F.: Ureteral reimplantation and bladder neck reconstruction. J.A.M.A., **175:** 349–353, 1961.

[3] Burns, E., Pratt, A. M. II and Hendon, R. G.: Management of bladder neck obstruction in children. J.A.M.A., **157:** 570–574, 1955.

[4] Herbut, P. A.: Urological Pathology. Philadelphia: Lea and Febiger, **1:** 52, 1952.

[5] Nesbit, R. M., Thirlby, R. L. and Raper, F. P.: Diagnosis and treatment of congenital urethral valves. J. Mich. Med. Soc., **50:** 1244, 1951.

[6] Gross, R. E.: Surgery of Infancy and Childhood, Philadelphia: W. B. Saunders Co., 1953, p. 733.

[7] Campbell, M.: Pediatric Urology. New York: The Macmillan Company, **1:** 336, 1937.

[8] Williams, D. I.: Urology in childhood. In Encyclopedia of Urology. Berlin: Springer-Verlag, 1958, vol. 15.

[9] Kjellberg, S. R., Ericsson, N. O., and Ruhde, U.: Lower Urinary Tract in Childhood: Some Correlated Clinical and Roentgenologic Observations. Chicago: Year Book Publishers, 1957.

[10] Young, H. H., Frontz, W. A. and Baldwin, J. C.: Congenital obstruction of posterior urethra. J. Urol., **3:** 289–354, 1919.

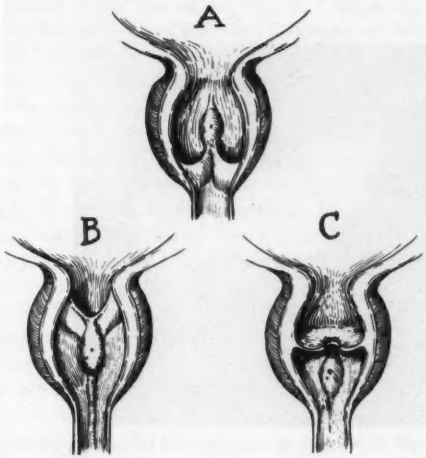


FIG. 1. Various types of posterior urethral valves. *A*, common; *B*, never encountered by authors; *C*, found only once.

the prostatic urethra and do not obstruct. The most common type is that indicated in figure 1, *A*; those represented by figure 1, *B* have not been encountered by us. A fourth group has been described in which there are combinations of the three presented in the sketch.

DIAGNOSIS

There are no distinguishing symptoms that will differentiate valvular obstructions from other types of bladder neck dysfunction in the infant. A clear concept of the variety of processes contributing to urinary bladder dysfunction is useful. We have found the following classification to contain the essential pathologic entities encountered in this area:

1) Urethral valves
2) a) Bladder neck obstruction (Marion's disease, contracture of bladder neck, congenital bar)
   b) Fibroelastosis
3) Megacystis syndrome
4) Neurogenic bladder

By bladder neck obstruction is meant stenosis of the vesical outlet alone, without a urethral valve or neurogenic disturbance. The condition is also known as Marion's disease or vesical neck contracture. It is regarded as being congenital. Fibrosis of the bladder neck is often present, and is a cause of obstruction. There is no evidence to show that infection is the primary cause of fibrosis. As a subdivision of congenital bladder neck obstruction we submit the entity described by Bodian[11] and termed fibroelastosis. This is a very unusual condition in which the obstruction is composed of tissue which on microscopic examination shows a large content of fibrous and elastic fibers. It has a further characteristic, in that the obstruction is not limited strictly to the level of the so-called internal sphincter, but rather extends throughout the entire length of the prostatic urethra down to and frequently beyond the verumontanum. As one can imagine, this condition is not readily corrected by the ordinary type of VY plasty.

In patients who have distal obstructions in the urethra, for example urethral valves, the bladder neck may become obstructive. This obstruction is not primary, but is secondary and is part of the general hypertrophy of the detrusor muscle in response to distal obstruction. It is important to distinguish secondary bladder neck obstruction from that arising primarily, as the operative treatment required in the two conditions is different. Resection or enlargement of a secondary bladder neck, leaving the primary site of obstruction intact, is an easy error to commit and we have presented in detail one patient in whom we did this.[12]

The megacystis syndrome[13] is characterized by the absence of any demonstrable obstructive lesion at the bladder neck in a patient with a very large bladder capacity and reflux. The trigone may be enlarged up to twice the normal size. Recurrent infection is common and progressive deterioration of the upper urinary tract may follow.

The neurogenic type of bladder will not be discussed here.

All the conditions mentioned in this outline have certain features in common. They produce death by progressive deterioration of the upper urinary tract due to hydronephrosis and hydroureter. Infection and chronic urinary retention are common. In the later stages as kidney

[11] Bodian, M.: Some observations on pathology of congenital "idiopathic bladder neck obstruction" (Marion's disease). Brit. J. Urol., **29:** 393–398, 1957.

[12] Hamm, F. C. and Waterhouse, K.: Changing concepts in lower urinary-tract obstruction in children. J.A.M.A., **175:** 854–857, 1961.

[13] Paquin, A. J. Jr., Marshall, V. F. and McGovern, J. H.: Megacystis syndrome. J. Urol., **83:** 634–646, 1960.

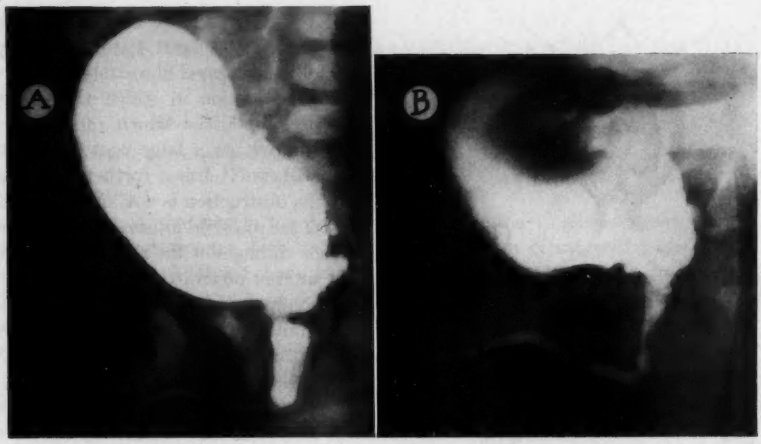


FIG. 2. Three-month-old patient with posterior urethral valve and development of secondary bladder neck. *A*, voiding urethrogram. *B*, same patient after transurethral removal of both valve and bladder neck. (Reproduced by courtesy of Dr. B. Berman, formerly chief resident, Kings County Hospital, now of Toronto, Canada.)

function diminishes, there is a failure to thrive, retarded growth and renal rickets. Reflux up the ureters may be present in either the valve or bladder neck type of obstruction, but it is not an early finding.

At cystoscopy all present a somewhat similar appearance. For example: the cord bladder, the bladder neck obstructions and the valve cases have a raised bladder neck and trabeculations are not unusual. The elevated bladder neck results from hypertrophy of the detrusor muscle. Diagnosis of valves of the posterior urethra by means of the cystoscope is difficult. The cusps of the valves point toward the bladder. As the instrument is introduced, these cusps are flattened out and are not readily seen through the cystoscope. Campbell and others have mentioned the importance of overdistention of the bladder and turning on and off the irrigating fluid, allowing it to pass down the urethra and dilate the cusps. We have not been successful with this maneuver. The voiding cystourethrogram has been the most important single procedure in our hands for demonstrating the presence of valves of the posterior urethra[14] (fig. 2). We have found that a voiding cystourethrogram is of great advantage in distinguishing between these four conditions. There is a tendency, unfortunately, for this examination not to be performed as it is thought to require expensive apparatus or to be difficult. The Swedish authors,[9] for example, have described their technique which requires an elaborate biplane, rapid changer and the child is supported in a special swing-like cradle. Lich[15] has described his method in which he uses a cinefluorogram and multiple spot plates. We have not found this to be necessary. No special equipment is required for our technique[16]:

1) The child is placed on the cystoscopic table and a plain film of the abdomen is made. The patient is then asked to void, after which a small rubber catheter is passed into the bladder and any residual urine is measured.

2) The bladder is filled to capacity with 30 per cent radiopaque material. This is more concentrated than usually used in simple cystography but is necessary to obtain satisfactory detail. It is essential that the bladder be filled well or time will be wasted in obtaining satisfactory x-rays.

3) The child is placed in the oblique position with the lower leg flexed and the upper leg straight. He is then encouraged to void and as soon as the patient is voiding to his maximum

[14] Griesbach, W. A., Waterhouse, R. K. and Mellins, H. Z.: Voiding cystourethrography in diagnosis of congenital posterior urethral valves. Am. J. Roentgenol., **82:** 521–529, 1959.

[15] Lich, R. Jr., Howerton, L. W. and Davis, L. A.: Vesicourethrography. Trans. Am. Assoc. Genito-Urinary Surg., **52:** 43–44, 1960.

[16] Waterhouse, K.: Voiding cystourethrography: A simple technique. J. Urol., **85:** 103–104, 1961.

capacity a single exposure is made. Care is taken that the child is voiding well, otherwise artifacts will be produced, due to partial closure of the sphincters. In a satisfactory voiding cystourethrogram, a good stream of urine should be seen issuing from the urethral meatus on the exposed x-ray film. In girls, we find it satisfactory to make voiding cystourethrograms in the lithotomy position. If the child is placed in the oblique position, the urine is diverted by the labia and unsatisfactory films result. Cystourethrograms can also be made in the newborn by filling the bladder and, if the baby is fed, he will usually void spontaneously. We have also obtained satisfactory voiding cystourethrograms following excretory urography. The child is kept in the out-patient x-ray department until sufficient radiopaque material is in the bladder and he wishes to void. This method is somewhat time-consuming and requires an alert nursing staff, but satisfactory x-rays can be obtained by this method.

The obstructing valve in the posterior urethra produces a typical voiding cystourethrogram. It is characterized by an elongation and broadening of the posterior urethra (fig. 2). In many instances the valve itself can be definitely seen in the lower part of the prostatic urethra. Evidence of hypertrophy of the detrusor is usually seen. The bladder neck may be wide open or it may be moderately to severely contracted by hypertrophy and encroachment of the detrusor muscle at the bladder neck. The bladder outline may be irregular, denoting the presence of trabeculations, cellules and small diverticula. Varying amounts of residual urine may be present. Acute urinary retention is unusual, as there is almost always some escape of urine through the valves.

FIG. 3. Use of infant resectoscope to trap valve by scraping lateral wall of prostatic fossa.

TREATMENT

Once the characteristic roentgenogram is found indicating the presence of valves, preparation can be made for their visualization with the infant resectoscope. This is a remarkably good instrument for this particular purpose. In the newborn it must be introduced through an external urethrotomy. In older children it can be passed through the entire urethra. Clear visualization is usually obtained with its ocular system and detection of the valve is facilitated by running the wire loop along the wall of the urethra (fig. 3). It is comparatively easy to resect the valves, using this technique. The valve is trapped between the loop and the beak of the sheath and the cutting current is switched on for only a fraction of a second, in order to sever the valve. The removal of valves by the endoscopic method has been superior to other procedures in our experience. Other methods of dealing with these valve-like formations have been suggested.

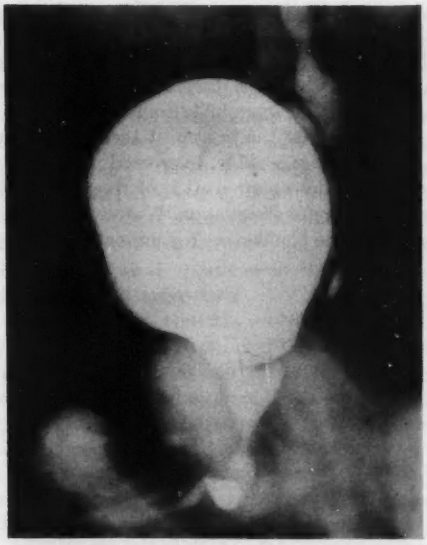


FIG. 4. Patient had posterior urethral valve. Secondary bladder neck is well shown. This had to be removed before suprapubic sinus would close.

Gross has indicated his preference for an exposure through the suprapubic area. He advocates separation of the symphysis pubis, and deep incision into the prostatic urethra. This type of operation was carried out in one of our patients with a satisfactory result. There may be times when this technique is indicated, but ordinarily the valves can be removed by more conservative surgery. Division of the symphysis can be done in the very young infant, but as the symphysis is separated considerable trauma to the sacroiliac joints could possibly occur in older children. Exposure of the prostatic urethra can also be carried out through a perineal incision, with an opening into the posterior or prostatic urethra, where the valves can be hooked with an instrument and severed with a scissors or a cutting current. We have not attempted this approach.

The question naturally arises, is it ever necessary to deal with the hypertrophied detrusor or a secondary type of obstruction that may occur at the bladder neck? It was necessary for us to perform a VY plasty in one of our early patients who had a valve, as an incomplete obstruction at the bladder neck prevented the suprapubic sinus from closing (R. W., fig. 4). In the presence of advanced destruction of the upper urinary tract, prolonged suprapubic cystostomy drainage may be indicated. However, we believe that in all doubtful cases, one should refrain from the use of the suprapubic tube. Recovery of the upper urinary tract has been discouraging following the use of prolonged suprapubic drainage.

To summarize the treatment then, we recommend, wherever possible, to proceed immediately with the endoscopic resection of the valves, followed by careful observation. We feel that hypertrophy of the bladder neck is muscular and once the obstruction is relieved, it should resolve. If there is evidence of secondary obstruction at the bladder neck proper, this should be dealt with either by endoscopic resection when practical, or by a VY type of plastic procedure.

Extensive deterioration of the upper urinary tract obviously reaches a point of no return in very much the same way as that observed in the elderly man as the result of chronic prostatic obstruction. At the present time we are inclined to allow the upper urinary tract ample time to show evidence of improvement, following the complete removal of obstruction of the bladder neck. Reimplantation of the ureter into the bladder has not been convincingly successful in the three instances in which we have employed it.

SUMMARY

Valvular obstruction in the posterior urethra in the infant is not rare. Its exact incidence is unknown but it is certainly greater than that recognized today.

The voiding cystourethrogram is a reliable method for the detection of this process. It should be done *before* cystoscopy and once a valve is suspected by its characteristic x-ray findings, it can be visualized with an instrument.

The resectoscope is used for visualization (through an external urethrotomy in the newborn). Two advantages accrue from this practice: a) The wire loop is useful in trapping and identifying the valve, and b) after trapping the valve in the loop, it can easily be removed by applying the cutting current.

Further surgery on the bladder neck and the upper urinary tract, plastic operations on the ureters, reimplantation operations, may be required later.

DISCUSSION

Dr. J. Hartwell Harrison (Boston, Mass.): May I ask a question? I think you have raised some imponderables, Dr. Hinman, especially with regard to an adult whom you were studying the first time. In this advanced state of chronic pyelonephritis, can we accurately differentiate between reflux that has occurred pursuant to pyelonephritis and that which is antecedent to it?

Dr. David M. Davis (Haverford, Pa.): I don't like to belabor this subject too much, but I would earnestly ask that as things are going now, that the time for definitive rationalization of these problems will be after the intraluminal pressure has been thoroughly studied.

One other point in connection with that: The pressure conditions found at the time of examination in any patient are not necessarily the same as they have been at times in the past. If there are abnormalities of ureteral function due to congenital changes, they may begin to do their harm while the individual is still in utero. The ureters are active in utero. Consequently, even in a young child, the consequences of ureteral abnormality may have been going on and developing over a long period.

Dr. Grayson Carroll (St. Louis, Mo.): I take it the essayists believe that the majority of these conditions are due to a weakness in the intramural portion, the back portion, of the bladder as the ureters come into the bladder. I would like to ask the essayists if they have used the Hutch operation and if it has been successful.

I am surprised that one of the essayists said that 20 per cent of all recurrent infection he found in children was due to regurgitation. I think that is a very high figure. I am very interested to know about how many patients that figure of 20 per cent includes?

Dr. John L. Emmett (Rochester, Minn.): It seems to me that this problem of obstruction of the vesical neck as the cause of ureteral reflux has been entirely overemphasized. So often, as you know, you see ureteral reflux unilaterally. Why? It has something to do with the ureterovesical junction.

Why do you see ureteral reflux so uncommonly in the ordinary case of benign prostatic obstruction? Usually when you see it, it is associated with a trabeculated bladder.

Also, why do you see ureteral obstruction so often in children with myelodysplasia in whom the bladders are almost empty all of the time and yet they have these enormously trabeculated bladders with cellular formation?

The other reason I am up here is to say this. Is Dr. Harry Spence here? I don't want to say this unless he is. Dr. Spence, I think that Dr. Hutch's idea and his fresh approaches to this subject here probably were played down a little too much at the American Urological Association meeting a year ago. I think that they were presented there; but it seems to me that his ideas about the cause of ureteral reflux are very pertinent and should be publicized a lot. It seems to me that his ideas represent very accurate thinking. Though I don't believe that we can prove it in every case, I think that it must be considered a lot more than we have considered it, as Dr. Hinman mentioned today.

Dr. T. Leon Howard (Denver, Col.): How do we open a door except by muscular power? How do we open our posterior sphincter except by muscular power? I think that in a lot of these cases Bell's muscle pulls the left ureter to the right ureter. At the same time, it opens the posterior sphincter. In my opinion, I don't think it's inflated. Occasionally you can get one of these patients to lie down for two or three hours with a full bladder. Regurgitation occurs without the act of voiding. But the cases that are frequently done—I mean most often done—you fill the bladder up and say, "Void." Bell's muscle, at the same time, pulls one of those ureteral openings open or both of them open at the same time. It empties the posterior urethra or at least the internal sphincter opens.

I don't think a word has ever been said about the effect of Bell's muscle, the interureteric ridge that goes from one ureter to the other; whether any work has been done on it at all. Yet I am quite sure that it is a factor in these cases of regurgitation.

Dr. Willard Goodwin (Los Angeles, Cal.): I would like to direct my remarks to Dr. Hinman. We have seen a patient with your syndrome who had staghorn calculus. I wondered if you had seen any calculi in your series of cases or if anyone else has.

The other thing I would like to ask is whether, in your opinion or anybody else's, pregnancy can be an initiating factor in this.

Dr. Wyland F. Leadbetter (Boston, Mass.): I certainly enjoyed these papers. I think that we are getting down to some semblance of brass tacks on this problem.

The thing that has bothered us most in caring for these children who have this particular problem is that every once in a while you find reflux on one side and don't demonstrate it on the other side only after you have carried out an operation for reflux which corrects it on that side, then blows up on the other side. I was wondering if you have any thoughts as to how we might recognize this and whether we can anticipate it and perhaps prevent a second operation on some of these individuals.

Then, in regard to the mechanism of reflux, although I certainly agree with Hutch's ideas on these things, I have observed one or two points that I think are of some significance. For instance, I have seen two patients who have had rather extensive denervation of the pelvis, one as a result of an attempt to clear symptoms of interstitial cystitis in which the doctor felt that the usual presacral neurectomy was not enough. He went ahead and did a much wider removal of nervous tissue, which obviously included part of the parasympathetic nerves supplying the bladder. Reflux occurred within the next two days. The patient came down with acute pyelonephritis. The x-rays showed the most remarkable development of reflux.

This makes me think that there may be more than one mechanism involved in this problem; perhaps several. This has been substantiated, in a sense, to my mind, by some of the work that one of our boys did in the laboratory. He studied the distribution of parasympathetic nerves in the pelvis and found that invariably in the dog there is a slip of nerve which goes to the lower ureter. If you divide that nerve—and you can show this on cineradiographic studies—if you divide the nerve, you can get immediate reflux on that side. If you stimulate the nerve, you get contraction of the lower end of the ureter almost immediately. It seemed to me, although we haven't substantiated the fact that this mechanism occurs in the human, that it is something like this which actually takes place.

I mentioned the operative effect of doing this and the fact that in a dog you can divide this nerve. I think the mechanism of the development of reflux is bound to vary from case to case. I think some of these cases of reflux are clearly the result of obstruction, decompensation, the effect of trigonal activity, which hasn't been mentioned except by Dr. Howard; and probably and perhaps the congenital deficiency of proper enervation of the lower ureter, and perhaps the associated area of bladder muscle.

Dr. Robert A. Garrett (Indianapolis, Ind.): I think that many of the questions that were first directed have been answered. We feel that the primary thinness of the bladder wall in these cases is probably of some significance, but we don't know why the wall is thin.

As far as the number of children involved, 20 per cent was 20 per cent of 149; but we have expanded the use of cineradiography recently, and I don't think that this is an accurate figure because we are beginning to do studies on children when they have their first attack of infection; whereas up to this time the studies were done only after repeated attacks had occurred.

With regard to the antireflux operation that I believe Dr. Carroll asked about, we are not prepared to go into any indications for the operation. I think that has to be worked out. But I am very happy about the results in those patients who have undergone the operation. No obstructions have been produced by the operation. All that we have done in the last few years have not regurgitated on the operative side. This was not true earlier.

Dr. Frank Hinman, Jr. (San Francisco, Cal.): (Slide) Since we are talking about mechanisms, here is a possible schema. Certainly it will help our thinking about it. Here is the usual pathway. This is pyelonephritis over here of the ordinary chronic variety.

But one can have, as Dr. Harrison raises the question, infection which then produces reflux through this mechanism so that you get an altered ureterovesical junction and then get reflux and, consequent upon that, chronic pyelonephritis. Similarly, though, one can have a primary vesical abnormality which then produces as part of it an altered ureterovesical junction. Whether this is due to neurogenic causes, primary anatomic causes, delayed maturation (as Dr. Hutch has suggested) is still not entirely clear. It is probable that there are several effects going on at once.

What I would like to emphasize is that in our

series of patients, one is dealing with the spectrum, the sequence going from one end of the rather typical patient with changes in the bladder wall, with saccule formation, and so on, to the other end, where there is no detectable abnormality, including, to answer Dr. Davis, changes in the warning pressure, which we do simultaneously with the voiding movies. There is no detectable change. I think we are dealing, to answer Dr. Harrison's question, with a much longer standing disorder than merely blood-borne chronic pyelonephritis, which then at some later time secondarily changes the ureter. Rather, in these younger people which are typical of this, I don't think it's right to call it a syndrome. We have removed that from the paper, even though it's in the title. I don't think it is that distinct; but in this group of patients, this upper route would seem to be the more reasonable one.

Dr. Carroll raises the question of the weakened intramural portion of the bladder and the effectiveness of the Hutch operation. Dr. Hutch isn't here, but I know how he would answer this, that the Hutch operation is effective in restoring the anatomic abnormality which has occurred by whatever mechanism, whether it has occurred from changes in the bladder wall and obstruction or by infection or by deficient innervation.

Dr. Emmett is right in saying that thinking about the ureterovesical junction primarily will lead us farther, as Dr. Hutch has evolved the mechanisms here, than thinking about the vesical neck, as we have in the past, or even thinking about infection itself and its consequences, even though obviously many areas can be abnormal.

Dr. Howard's question regarding Bell's muscle: An active Bell's muscle would be expected to pull down the orifice. Obviously this would decrease reflux, elongating the intermural ureter. Disease of Bell's muscle would be expected to lead more to reflux. This is believed to be part of the explanation for neurogenic reflux and also for that occurring after long-standing infectious changes.

Dr. Goodwin asks regarding staghorn calculi. None of our patients had calculi. Their kidneys merely went on to extreme atrophy. The average weight of these three kidneys was 30 gm.

Pregnancy has initiated the symptoms in two of our patients, in one of whom, we believe, pregnancy had nothing to do with the reflux changes because this patient had a saccule, indicating that there had been a developmental defect of long-standing vesical abnormality rather than some change which could have occurred during pregnancy itself. This is one example, and that doesn't answer the question categorically.

Dr. Leadbetter's comments on why does reflux occur on the opposite side after operation: I think in part, as we have observed in some of our patients, this is due to faulty operation the first time. Cystoscopy was not done often enough or long enough during the initial observation. Consequently, one couldn't say. I think it's easy enough to say that a patient has reflux; but the burden of proof is on him who says the patient doesn't have reflux. Sometimes repeated studies are required.

The other is that operation often doesn't clear up the infection so that there can be further changes which could lead to reflux afterwards.

URETHRAL STRICTURES IN MALE CHILDREN

GUY W. LEADBETTER, JR. AND WYLAND F. LEADBETTER

From the Massachusetts General Hospital and Harvard Medical School, Boston, Mass.

Urethral strictures in male children are uncommon but not rare. The literature contains only 8 case reports and is generally devoid of methods of treatment with careful followup studies. The etiology of urethral stricture in children may be congenital, infectious or traumatic. The congenital stricture may be located at single or multiple positions anywhere in the urethra and is probably due to embryologic narrowing of the channel or, in atresia, failure of tube formation. There is no pathologic evidence of sclerosis in the stenosed area unless secondary infection or trauma has developed from instrumentation. Campbell[1] found atresia of the urethra 4 times in 19,046 autopsies. Engel[2] reported a case of death in the newborn from urethral atresia. At autopsy the kidneys and ureters were markedly dilated. The urethral atresia located just distal to the membranous urethra was 1.5 cm. in length but beyond this, urethral caliber was normal. In our series, 2 patients are presumed to have had congenital strictures 0.5 to 1.5 cm. in length and located proximal to the fossa navicularis.

Infectious strictures in children have been reported as due to gonorrhea only, by Alvarez Colodrero[3] and Nobecourt.[4] We have seen none. The infectious type is commonly found in the pendulous or bulbous portions of the urethra because here there are many crypts and glands where bacteria may reside and multiply. If untreated, urethritis and periurethritis result in scarring and stenosis.

Traumatic strictures may be due to an operative procedure or external injuries. Transurethral resection, urethroplasty or instrumentation may all cause strictures which are usually located distal to the bulbous urethra. Injury of the urethra commonly occurs following straddle injury of the perineum or by direct trauma such as a kick or a gunshot wound to any portion of the urethra. Straddle injuries usually result in stricture of the bulbous area, although one of our patients fell while tree climbing, bent and injured his penis with resultant stricture formation of the midshaft area. The mechanism of urethral and periurethral scarring following trauma in operative procedures is probably similar. This must result from hematoma formation and/or local urinary extravasation followed by a local inflammatory process which may be aggravated and accelerated if secondary infection occurs.

The symptoms encountered in patients with stricture formation are those of obstruction. Symptoms from congenital stricture often do not become obvious until the age of two or three, and because the development of traumatic stricture is gradual, early symptoms often go unrecognized. It is not until the patient strains to void, takes a prolonged period to empty the bladder, produces a weak stream or even just a few drops, that a physician is consulted. Sometimes, intervening infection calls the problem to the attention of the physician earlier.

The diagnosis may be suspected from the history but is best confirmed by cystourethrography. If the urethra will not accept a catheter, retrograde urethrography should be performed. It is important that x-ray evaluation be done prior to any treatment, particularly dilatation, so that the exact degree and extent of the lesion can be demonstrated. During evaluation any instrumentation of the urethra with bougies, sounds or cystoscopes should be attempted only with anesthesia. If the discomfort produced during these procedures should cause the unanesthetized child to move suddenly, additional and irreparable urethral damage may occur. The characteristic retrograde urethrogram shows dilatation distal to the stenosed areas while the voiding cystourethrogram (fig. 1) demonstrates dilatation of the urethra and sometimes the bladder neck

[1] Campbell, M. F.: Stricture in children. J. Pediat., **35:** 169–179, 1949.

[2] Engel, W. J. and Schlumberger, F. C.: Urinary extravasation in new-born infant associated with congenital stenosis of urethra; report of case. Cleveland Clin. Quart., **5:** 278–283, 1938.

[3] Alvarez Colodrero, J. W. and di Lella, P.: Gonorrheal intractable stricture of male urethra in childhood; 3 cases. Rev. de especialid, **4:** 429–431, 1929.

[4] Nobecourt: Chronic gonococcal pyelonephritis and urethral stricture in boy 13 years old; case. Rev. Gen. de Clin. et de Clin. et de Therap., **46:** 785–789, 1932.

FIG. 1. Stricture of distal urethra. Dilatation of posterior urethra and bladder neck.

proximal to the area of stenosis. Direct visualization of the stricture may sometimes best be performed with the infant panendoscope which allows visualization of the diseased area and an accurate estimation of the degree and extent of the stricture prior to dilatation.

Untreated or inadequately treated urethral stricture may become associated with chordee, chronic prostatitis, epididymitis, contracture of the bladder neck, decompensated bladder with residual urine, pyelonephritis, vesical calculus and, more readily, hydroureter, hydronephrosis, renal damage and even death. Campbell[5] has emphasized these facts in the past. These sequelae in untreated or inadequately treated strictures may by no means be uncommon. The trauma or the introduction of infection, which results from repeated dilatation, increases these complications. Information relative to the methods of treating urethral stricture in children is almost totally absent from the literature. Campbell emphasizes the necessity of treatment and lists the methods available as dilatation, internal and external urethrotomy. Lowsley and Kirwin[6] advocated urethral dilatation only. Neither author mentions the frequency of dilatation required nor the eventual outcome of such treatment. During the past 3 years, we have encountered 6 children with urethral strictures and 2 adults in whom strictures developed following an accident in their teens. The two adults are included to emphasize complications which may occur during a long period of treatment by dilatation. In this series, two strictures are presumed to be congenital, four followed trauma (three straddle injuries, one a kick) and two followed operative procedures (one a hypospadias repair by free graft technique, and one followed instrumentation). All patients have had adequate trial of dilatation but have subsequently been surgically treated. Five have had a two stage modified (Leadbetter) Johanson urethroplasty, two have had the first stage only, and in one, the one stage technique to be presented. The technique of the two stage modified (Leadbetter) Johanson procedure has been described.[7] Because there is not sufficient skin in the distal one third of the urethra, the one stage urethroplasty to be described is limited to strictures 3.5 cm. or less in length and those located in the bulbous and proximal penile urethra.

[5] Campbell, M. F.: Clinical Pediatric Urology. Philadelphia: W. B. Saunders Co., 1951.

[6] Lowsley, O. S. and Kirwin, T. J.: Clinical Urology, 3rd ed. Baltimore: The Williams and Wilkins Co., 1956, pp. 280–281.

TECHNIQUE

When urethroplasty is contemplated, it is important NOT to dilate the urethra, for if the urethra has been recently dilated, the exact extent of the disease may be difficult to determine. The stricture is easily located when the area is tight.

When the stricture is located in the bulbocavernous area, the inverted U incision with Y extension up the scrotal raphe, as described in a previous article,[7] is made. If the stricture is more distal, a longitudinal incision in the scrotal raphe is used. The incision is carried down to the urethra, the sound is passed to the initial point of obstruction and the urethra entered over the sound. The incision is extended distally 0.5 to 1 cm. into the normal urethra and proximally to open the entire area of stricture and 0.5 to 1 cm. into the proximal normal urethra. All periurethral scar is excised. Hemostasis must be meticulous. Size 5-0 and 6-0 chromic catgut is used for suture ligation of bleeding vessels. Next, an incision is made (fig. 2, *A*) in one lateral skin margin to form an elipse of skin about 1 to 1.5 cm. wide, i.e. about the width of desired urethral diameter. Care is taken not to divide the subcutaneous blood supply of the pedicle flap. The flap itself is not undermined but rather, the

[7] Leadbetter, G. W.: A simplified urethroplasty for strictures of the bulbous urethra. J. Urol., **83:** 54–59, 1960.

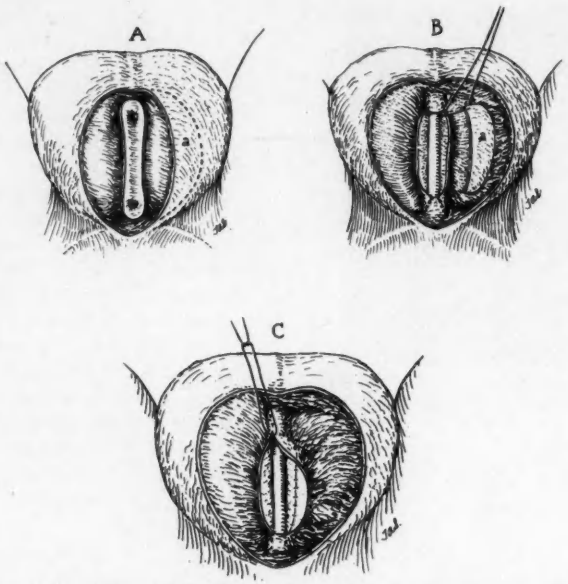


FIG. 2. *A*, formation of pedicle scrotal flap to cover urethra. *B*, beginning of anastomosis of flap and urethral edge. *C*, completion of second edge of flap anastomosis.

lateral incision edge. By this technique the flap with subcutaneous blood supply intact may be sufficiently mobilized. The two adjacent margins, i.e. the skin and urethra, are carefully approximated with size 6-0 chromic catgut sutures. Knots must be tied on the outside. Sutures must be close together to insure accurate approximation (fig. 2, *B*, *C*). Next, a small catheter is placed through the urethra into the bladder (size 6-8F in children, 14-16F in adults). We have not used the diverting suprapubic cystotomy or proximal urethrostomy although it may be desirable in some cases. It should be done if a urinary tract infection is present. After completion of one side of the anastomosis (fig. 2, *C*) the flap is inverted so that the skin surface will line the new lumen. The anastomosis of the remaining edge of the flap and the urethra is completed. The fascia, subcutaneous tissue and skin are carefully closed.

We stress the use of a multiple, staggered, layered closure of fascia, subcutaneous tissue, bulbocavernosus muscle (if involved) and finally skin. If skin and subcutaneous tissue only are closed, diverticula of the new urethra may result. In a series of 35 adults and 6 children, we have had only one small fistula and no diverticula, a result we believe related to multiple layered closures. After completion of the closure a pressure dressing is applied for 3 days. This prevents edema formation and controls any residual capillary ooze. The catheter is removed six to eight days later.

CASE REPORTS

Case 1. G.H. (MGH No. 1058921). A 65-year-old man was kicked in the genitalia at the age of 14. He did not have significant difficulties at this time but several years later he fell from a bicycle and ruptured his posterior urethra. Following this accident, he had difficulty in voiding and until his recent operation, required monthly dilatation. During the ensuing years, he has had recurrent urinary tract infection, epididymitis which required orchiectomy; prostatitis and significant chordee which made intercourse difficult and painful. The voiding urethrogram is shown in figure 3. On admission to the Massachusetts General Hospital 1½ years ago, a first stage urethroplasty was performed. Several months later, residual chordee necessitated revision of the first stage procedure. Following this, because of persistent urinary tract infection, a third procedure consisting of removal

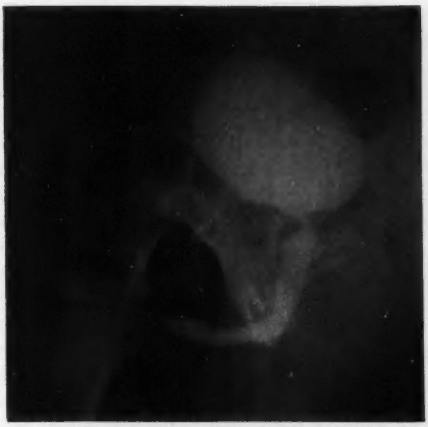


FIG. 3. Case 1. G. H., No. 1058921. Voiding urethrogram shows distal penile stricture and proximal dilatation. Note marked bladder neck obstruction and bladder diverticula.

of a fibrous prostatic adenoma, revision of the bladder neck and diverticulectomy had to be performed. At the present time, 3 months later, the urinary infection has been eliminated. He has no difficulty with intercourse and the final stage of the urethral reconstruction is contemplated.

Case 2. F.S. (MGH No. 1136870). A 64-year-old man, following a straddle injury at age 16, had a posterior urethral stricture that required dilatation every three to four months. He gave no history of pyelonephritis, chills or fever, but he did have a small, weak urinary stream with a prolonged emptying time and persistent lower urinary tract infection. Four years prior to admission, a urethral reconstruction was accomplished by resection and reanastomosis of the strictured area. The stricture recurred and dilatation was again necessary. Because dilatation had been required every four or five days during the 3 months prior to admission, further surgical repair was reconsidered. Preoperative studies revealed a normal intravenous urogram, a coliform infection and no residual urine. A cystourethrogram (fig. 4) demonstrated a 4 cm. bulbopenile stricture which would accept only a size 10F catheter. Since performance of a first stage modified (Leadbetter) urethroplasty, he voids without difficulty. Second stage reconstruction is to be completed in four to five months.

Case 3. J.F. (MGH No. 993270). An 8-year-old patient was admitted to the Massachusetts General Hospital because of acute pyelonephritis. He had had no previous instrumentation or injury. Urine studies revealed many white blood cells with clumps and a coliform infection. The residual urine was 3 cc. His intravenous urogram was negative. Cystoscopy was performed and the urethra dilated to a size 18 sound with some snugness. Cystoscopic examination was normal. However, following the examination he experienced difficulty in voiding and a cystourethrogram (fig. 1) showed narrowing of the distal end of the penile urethra. This was treated by redilatation of the urethra and placement of an indwelling catheter. The catheter was removed

FIG. 4. Case 2. F. S., No. 1136870. Cystourethrogram shows mid-penile and posterior stricture. Note irregularity of urethra.

FIG. 5. Case 3. J. F., No. 993270. Preoperative cystourethrogram shows dilatation distal and proximal to stricture.

4 days later and the patient discharged. Two months later he returned complaining of dysuria, frequency and difficult voiding. Urine culture was again negative. At cystoscopy the urethra accepted a size 12 sound but sizes 14 and 16 were extremely tight. A cystourethrogram demonstrated a stricture at the distal urethra. The catheter was again left indwelling for 4 days and over the next 1½ years, he apparently remained asymptomatic. However, just prior to his most recent hospital admission, symptoms of obstruction recurred and Streptococcus hemolyticus was cultured from the urine. Residual urine was 30 cc. Intravenous urography was normal. A retrograde cystourethrogram revealed (fig. 5) a tight stricture in the midshaft of his urethra. This was almost certainly due to instrumentation at the time of the initial cystoscopy. Operation was performed for correction of this stricture by the one stage technique and the child, now only two to three weeks postoperatively, has had an uneventful convalescence.

Case 4. R.F. (MGH No. 1083958). At age of three this child experienced frequency and difficulty in voiding. He had no history of instrumentation or trauma; a diagnosis of urethral stricture was made. Over the next 6 years two internal urethrotomies and multiple urethral dilatations were performed. The patient continued to have symptoms and was admitted to the Massachusetts General Hospital for evaluation. Studies of the upper urinary tract and renal function were within normal limits. A cystourethrogram demonstrated stricture of the distal urethra. The urine was sterile even in the presence of 150 cc residual urine. A first and second stage Johanson-type urethroplasty was completed. His stream has remained excellent and there has been no residual urine or infection. A postoperative cystourethrogram showed an adequate urethra. The etiology of this stricture is presumed to be congenital.

Case 5. P.M. (MGH No. 1106565). A 3-year-old white boy had marked difficulty starting his urinary stream 1 day prior to admission. The mother said that the stream was weak and denied previous difficulty or any incident of trauma or instrumentation. The urine was sterile and the residuum nil. An intravenous urogram was normal. Under anesthesia, an obstruction proximal to the fossa navicularis prevented cystoscopy. Cystoscopic examination, performed after the urethra was dilated with filiforms and followers, was negative but a 0.5 cm. stricture at the distal end of the penile urethra was noted during examination with the panendoscope. A size 8F catheter was left indwelling for 3 days. Following removal, the child voided well although shortly after being discharged, he again experienced difficult, painful voiding. Despite intermittent relief of pain with medication and treatment by three subsequent dilatations, symptoms of painful, difficult urination remained. Because of persistent symptoms, a first stage urethroplasty was performed. For the first time since the onset of symptoms he was comfortable and voided without difficulty or pain. Five months later, the urethral reconstruction was completed and since then, voiding has been normal. The urine is sterile. Etiology of this stricture is presumed to be congenital.

Case 6. B.W. (MGH No. 81029). At age of 6 years this child presented with a penile hypospadias associated with chordee. A first stage correction of the chordee was performed but 5 months later recurrent chordee necessitated a revision. Four months following this, a second stage closure was performed by using a nonpedicle, full thickness graft of circumcised skin. This graft was formed into a tube which was placed through the glans and down to the area of the proximal urethra at the penoscrotal junction. Anastomosis of the proximal urethra and graft was done at this time. Three months later, final reconstruction and reanastomosis of the proximal urethra and the previously formed urethra were accomplished. Three months following this, a severe urethral stricture, complicated by epididymitis, developed. Subsequently, excision and reanastomosis of the stricture were performed. Despite this effort, frequent urethral dilatations were necessary over the next 5 years. He continued to have enuresis, urinary infection and residual urine of 75 to 125 cc. In June 1959, a first stage Johanson procedure was performed. The urethra and the strictured area were incised and heavy periurethral scar removed. Two months later, a band of scar developed along margins of the previous skin-urethral mucosa anastomosis necessitating revision using much finer (size 6-0) chromic catgut. Following revision, the area healed soft and pliable. The proximal

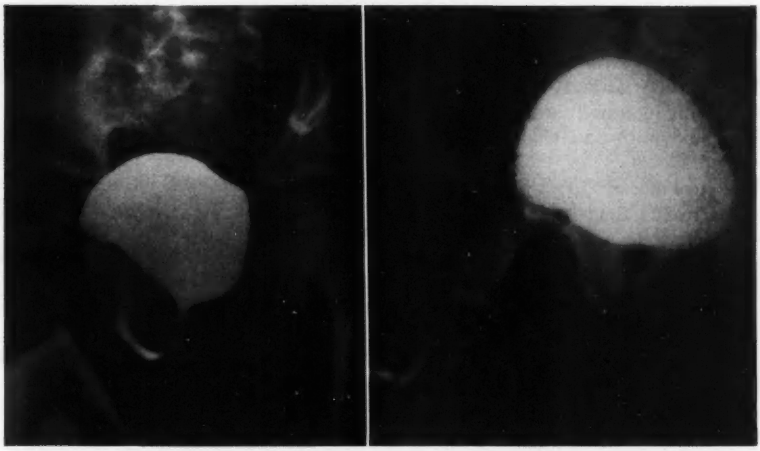


FIG. 6. Case 8. R. W., No. 627999. *A*, voiding cystourethrogram demonstrates stricture in area of bulbous urethra. *B*, voiding urethrogram demonstrates postoperative patency of urethra.

urethra remained patent and accepted a size 18 sound. One year later, in June 1960, the final stage of urethroplasty was completed. The child has been asymptomatic. His urinary stream is excellent. There is no residual urine and the urine is sterile.

Case 7. S.C.C. (MGH No. 1020090). At age of 6 years this child fell from a tree straddling a limb below and bent the end of his penis. At age of nine, in July 1958, he presented with symptoms of frequency, dribbling, burning and difficult urination. The onset of his symptoms had been gradual and only recently noted. Residual urine (150 cc) was infected with nonhemolytic Streptococcus. An intravenous urogram was normal. A cystourethrogram revealed a stricture at the midshaft of the penis. A first stage urethroplasty was performed in August 1958. One year later, the second stage reconstruction was completed. Two years after operation the patient has no symptoms and voids with a good stream. The urine is sterile and no residual urine is present. A cystourethrogram is normal and no dilatations have been required.

Case 8. R.W. (MGH No. 627999). This patient fell while climbing a tree at the age of 8 years, straddled a limb and sustained an injury to the perineum. Following this accident he noticed gradual onset of urinary frequency, dysuria and enuresis. He was admitted to the hospital in May 1957. An intravenous urogram was normal. One hundred fifty cubic centimeters of urine were present and contained coliform bacteria. A cystourethrogram (fig. 6, *A*) confirmed the presence of a stricture in the bulbous portion of the urethra. First and second stage urethroplasties were performed by the modified Leadbetter technique. Following the second stage, the patient was improved but a recurrent stricture developed at the proximal end of the repair. The patient was re-explored 1 year later, the strictured area incised and the pedicle flap procedure performed. Following this he has remained asymptomatic. The urine is sterile and no residual urine is present. A urethrogram (fig. 6, *B*) demonstrates an adequate urethra.

FINAL COMMENTS

The two adults are included to emphasize that long term dilatation is not a satisfactory solution to the stricture problem. Patient G.H. (case 1) had many complications and prior to corrective surgery, was becoming increasingly worse. Patient F.S. (case 2) had persistent urinary tract infection and required increasingly frequent dilatation. Following the first stage urethroplasty, both patients were relieved of symptoms and have had no further complaints. From results obtained thus far, we believe that urethroplasty, as described, has a definite place in the

treatment of urethral stricture in children. Operation is indicated when several dilatations of the urethra fail to solve the problem. By performing operations early, it is hoped that the complications of increased scarring, chordee, prostatitis, epididymitis and bladder difficulties can be avoided.

We have completed urethroplasty on 6 children. The results thus far have been satisfactory. No further dilatation has been required and urinary infection has been eliminated.

SUMMARY

The cases of 8 patients are presented in whom urethral stricture developed in childhood. Two of these were adults.

A surgical technique for urethral stricture is presented.

Surgical treatment of urethral strictures in children is urged after an adequate trial of dilatation has failed.

The results have been satisfactory.

THE GENESIS OF BENIGN POLYPS IN THE PROSTATIC URETHRA

REED M. NESBIT

Twenty years ago, while performing endoscopy upon a 30-year-old physician for the inspection of a congenital anomaly of the urethra, the author fortuitously discovered that the patient's prostatic urethra was covered with a most unusual lining. It looked like pink velvet and this appearance prevailed throughout the entire area. Biopsies were reported as follows: "A small papillomatous structure covered by columnar epithelium. This epithelium can be explained only upon the basis of a developmental disturbance. No malignancy."

Sections of the tissue were sent to Dr. Frank Hinman, then professor of urology at the University of California Medical School, and to Dr. Hugh Young at Johns Hopkins Hospital. Both of these men later reported that the pathologists in their institutions shared with them the belief that the tissue was not neoplastic, but they were not able to identify the epithelium or explain its presence in the prostatic urethra. The patient has never had any symptoms arising from the structures in question.

About a year after this first experience another physician, aged 32 years, complained of passing two small blood clots from the urethra. There were no other symptoms or signs. Endoscopy revealed no abnormality of the bladder but on the floor of the distal prostatic urethra, on either side of the verumontanum, there were several small polyps that had the appearance of tiny papillary neoplasms. Biopsies were taken and the lesions fulgurated with the high frequency current. Our pathologists reported that the tissues were identical in appearance to the polyps that had been found in the first patient, and again asserted the belief that a developmental disturbance was responsible for the unusual abnormality.

A review of the literature concerning lesions of this sort in the prostatic urethra provided a number of reports that described such polyps but no author explained the nature or identity of the epithelium.

In the hope that the perspective of the embryologist might help to solve the mystery Dr. Bradley Patten was consulted. In fact, the first discussion regarding the matter was held during a social occasion and the author described the epithelial cells as being tall columnar cells with nuclei near the base, and having clear cytoplasm, and said that to his inexpert eye they somewhat resembled gallbladder epithelium. Professor Patten immediately speculated upon the matter and predicted that they would turn out to be aberrant prostate gland epithelium. When he later examined the tissue sections (fig. 1) he expressed the belief that the columnar cells were indeed prostate gland epithelium and proposed the theory that the polyps represent an upward projection of the epithelial elements so that a frond-like arrangement occurs in contrast to the usual growth pattern of this epithelium which ordinarily forms itself into an acinar gland structure by downward growth from the urethra.

The columnar epithelial cells of the urethral polyps are taller than the cells in the prostatic acini and Professor Patten has explained this difference on the basis of environmental pressures: glandular secretions probably generate enough tension within the acini to inhibit the lining epithelium from attaining as much height as is attained in the urethra where such pressure is lacking.

The pathologists in our medical school accepted these explanations of our eminent professor of anatomy and since then have described the lesions as being made up of aberrant prostatic epithelium.

A total of twelve such cases have been seen and biopsies obtained; all the patients except the first one had polyps that resembled papillary tumors, usually situated on the floor of the prostatic urethra. In two instances the polypi arose, tuft-like, from the verumontanum. The age incidence has ranged from 24 to 65 years.

All cases except the first one had bleeding, either gross initial hematuria or else microscopic hematuria. In three instances there was some dysuria not associated with infection and one patient who had dysuria also complained of frequent nocturnal erections. One patient noticed drops of blood at the urethral meatus immediately following coitus but had no hematuria and no hematospermia.

These cases have been so few in number and have come along so infrequently that efforts to

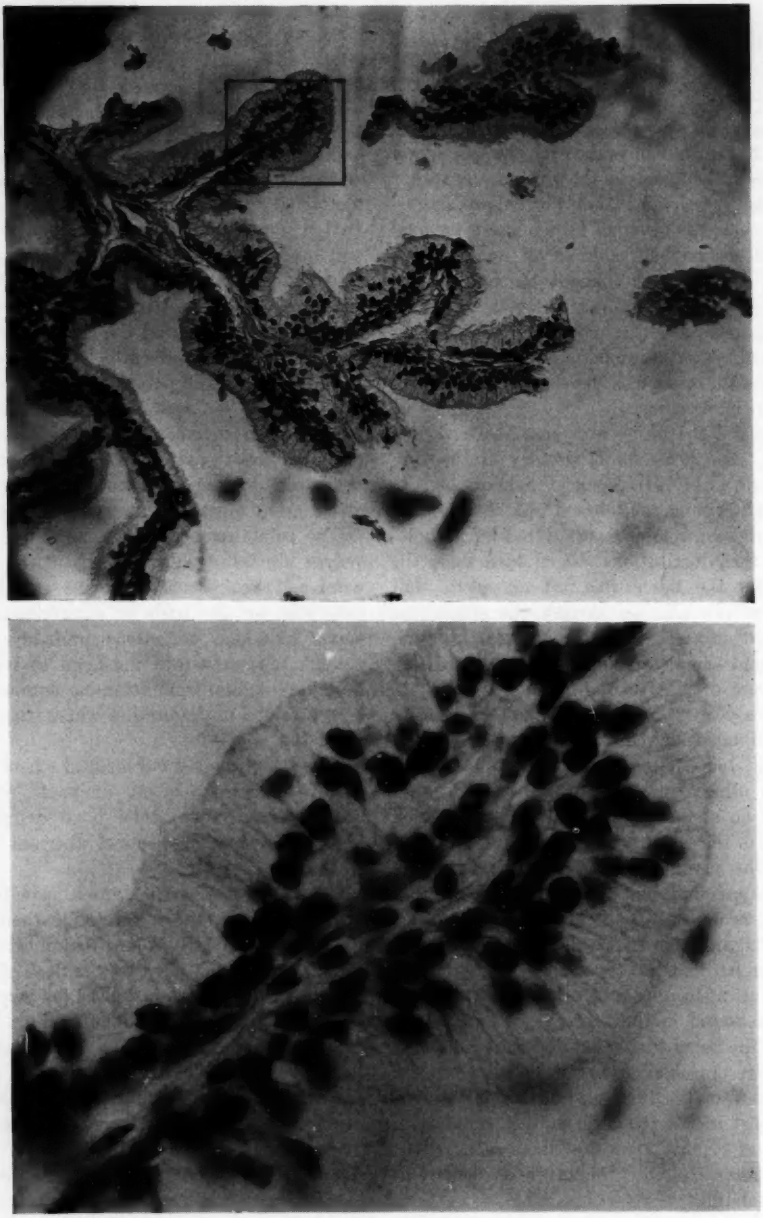


FIG. 1

establish the identity of the tissue with finality, using stains to identify acid phosphatase, have been difficult. Three years ago a patient presented symptoms that suggested the condition so preparations were made in the Department of Pathology for Gomori's staining. The result was thought to be positive for identification of acid phosphatase in the cells but some question arose in

the mind of the pathologist regarding his use of the technique so he decided that the test was only highly probable and not definitely positive.

Recently two such cases have been examined in which the diagnosis was suspected from the history so the pathologist was prepared in advance to process the fresh tissues for staining with the standard Azo dye technique. As a control, fresh prostate gland tissue was simultaneously stained. In each case both tissues, the urethral polyp and the prostate gland epithelium revealed brown staining of the cytoplasm which characterizes the presence of acid phosphatase.

This then provides positive proof concerning the identity of the columnar epithelium in question and substantiates Professor Patten's theory that the polyps are composed of aberrant outgrowths of prostate gland epithelium.

SCROTAL AND PENILE LYMPHEDEMA

GEORGE J. BULKLEY

From the Urologic Services of Chicago Wesley Memorial Hospital and Veterans Administration Research Hospital, Chicago, Ill.

The term lymphedema is used to describe the swelling which occurs secondary to imperfect drainage of lymph from the tissues. Lymphedema is characterized by a soft pitting edema and preservation of fairly normal skin which may be stretched thin by the subcutaneous collection of fluid. It is a reversible condition following removal of the etiologic agent. Elephantiasis is an essentially irreversible state characterized by hard, brawny edema and a rough, thickened skin resembling that of an elephant. It is the result of fibrous organization, loss of elastic fibers, hyperplasia of collagenous connective tissue and frequently secondary bacterial infection of the skin and subcutaneous tissue.[1] Elephantiasis is generally thought to be the endstage of chronic lymphedema plus some superimposed infection which causes permanent tissue changes.[2] The progression of chronic lymphedema into an irreversible state is usually a gradual one, and proper therapy depends upon recognition and differentiation of reversible lymphedema from elephantiasis.

Lymphedema and elephantiasis of the penis and scrotum may constitute a major disability requiring surgical correction, and we have recently had several patients with this condition under our care. Although such instances are uncommon in this country, elephantiasis of the scrotum as the result of chronic filarial lymphedema is frequently seen in the tropics and is reported to affect 20 per cent of all males in some regions.[3] DeSavitsch reported that scrotal elephantiasis accounts for one operation in seven in Stanleyville in the Belgian Congo.[4] Such scrotal enlargements may reach huge proportions and present a real problem in surgical logistics due to size alone. The largest reported scrotal mass removed is said to have weighed 226 pounds, and weights of over 100 pounds of scrotal tissue removed are not uncommon.[5] Overhead pulleys for retraction of the huge mass are necessary, and the use of a tourniquet to control blood loss is often required. For the latter purpose, one author has found the bicycle inner tube the best available tourniquet.[6] Such bizarre instances as the patient who required a wheelbarrow to transport his own scrotum are not seen in the United States, but the principles of treatment of elephantiasis tropicum are essentially the same as those applied to elephantiasis nostras (meaning "of our country").

[1] Matas, R.: Am. J. Trop. Dis., **1:** 60, 1913.

[2] a) Muller, G. P. and Jordan, C. G.: Ann. Surg., **97:** 226–236, 1933. b) Commando, H. N. and Echikson, J. I.: Am. J. Surg., **58:** 264–266, 1942. c) Manson-Bahr, P. H.: Tropical Diseases. New York: Wm. Wood & Son Publ., 1921, p. 621.

[3] DeGreef, R.: Ann. Soc. Belge de Med. Trop., **18:** 5, 1938.

[4] DeSavitsch, E.: J. Urol., **45:** 216–222, 1941.

ETIOLOGY

A. Primary or idiopathic
   1. Congenital (Milroy's disease)[7]
   2. Lymphedema praecox (developing at puberty)[8]

B. Secondary or obstructive
   1. Inflammatory
      a. Filarial (tropical, leading to elephantiasis)
      b. Lymphogranuloma, chancroid, tuberculosis, syphilis, erysipelas and leprosy[9]
   2. Surgical
      a. Lymph node dissection of inguinal region
      b. Scars in the groin
   3. Carcinoma with blockage of the lymphatics
   4. Post-irradiation destruction of lymphatics

[5] a) Windell, J. T.: Internat. J. Surg., **29:** 114, 1916. b) Watson, E. M.: J. Urol., **36:** 786–800, 1936. c) Kellensberger, E. R.: J.A.M.A., **82:** 1197, 1924.

[6] Ouzilleau, E.: Presse méd., **31:** 617, 1923.

[7] a) Milroy, W. F.: N. Y. Med. J., **56:** 505, 1892. b) Milroy, W. F.: J.A.M.A., **91:** 1172, 1928.

[8] Allen, E. V.: Arch. Int. Med., **54:** 606, 1934.

[9] a) Gougerst, H.: Presse méd., **33:** 1121, 1925. b) Marshall, C. H.: J.A.M.A., **85:** 875, 1925. c) Muccini, G.: Policlinico, **32:** 1117, 1925. d) Stryker, G. U. and Plock, B.: Arch. Derm. & Syph., **32:** 86–89, 1935. e) Windell, J. T.: Surg., **29:** 114, 1916.

FIG. 1. Case 1. Jean Baptiste Authier, aged 35, prior to surgery in 1820

5. Medical
   a. Cardiac or renal failure
   b. Venous thrombosis
   c. Hypoproteinemia

Primary lymphedema is occasionally congenital, but more often occurs during childhood or adolescence and is called lymphedema praecox. Such instances usually involve the lower extremities and genital edema is not a serious problem. The recent development of lymphangiography has helped classify the etiology of primary lymphedema. Injection of dye or radiopaque materials into the lymphatics of patients with primary lymphedema has shown that the essential defect is a deformity in the anatomy of the lymphatic channels in most cases.[10]

Secondary lymphedema is always obstructive, and proper therapy depends upon the correct diagnosis of the obstructive factor. This is not usually difficult. The most frequent cause of secondary lymphedema is an inflammatory episode with blockage of the lymphatic channels secondary to infection. The inflammation may be very low grade and unrecognized, as in one of the cases reported here. In this country, lymphogranuloma, chancroid, tuberculosis and erysipeloid streptococcal infection probably account for the majority of cases of scrotal and penile lymphedema. Tropical elephantiasis is, of course, most commonly filarial in origin and accounts for the large numbers of patients seen in these areas.

Surgical secondary lymphedema is often the result of radical surgery of the inguinal area, as in a radical groin dissection. Such lymphedema usually involves the entire lower extremity on the operated side, and is partially irreversible, although new lymphatic channels may form in time to improve drainage of the limb and genitalia.

Carcinoma with blockage of the lymphatics is a common cause of lymphedema in the groin, and frequently genital lymphedema is a serious problem in these instances. Post-irradiation destruction of lymphatic drainage is usually seen concomitantly with carcinoma, since the triad of surgery, carcinoma and irradiation frequently goes together, as illustrated by one of our patients reported here.

The "medical" causes of lymphedema are important to distinguish from other obstructive causes, since treatment here depends primarily upon the treatment of the essential pathology which may be cardiac failure, renal failure, or venous thrombosis. Venous stasis following thrombosis leads to severe damage to the skin and subcutaneous tissue, and any surgical therapy in such an area is doomed to failure. Lymphatic stasis alone has much less serious consequences, for the fault is chiefly confined to the defective removal of protein alone, whereas venous stasis leads to faulty removal of all elements from the tissue spaces. This is why the skin overlying areas of lymphedema may remain in good condition for long periods of time, and may often be used as a secondary graft.[11] The lymphedema which occurs secondary to the "medical" causes is nearly always reversible, and, therefore, seldom requires surgery.

SURGICAL TREATMENT

The surgical approach to the treatment of lymphedema and elephantiasis may best be divided under two general headings. The first is the "physiologic" approach, which has as its purpose the removal of obstruction, correction of the circulatory defect, and an attempt to establish new lymphatic channels. The physiologic method

[10] McKee, D. M. and Edgerton, M. T. J.: J. Plast. & Reconst. Surg., **23:** 480–492, 1959.

[11] Editorial comment: Brit. J. Plast. Surg., **7:** 193, 1954.

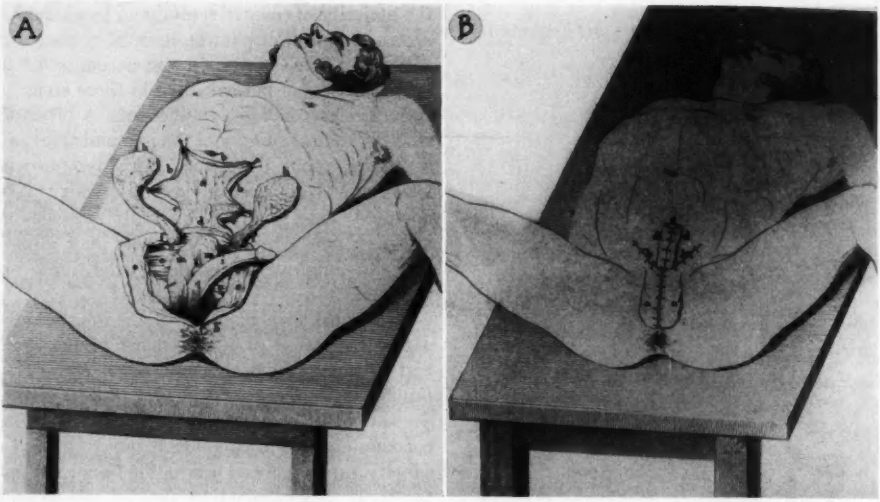


FIG. 2. Case 1. *A*, surgical exposure after removal of excess tissue by Prof. Delpech indicating skin flaps for reconstruction of penis and scrotum. *B*, completed closure after more than 90 minutes of surgery without benefit of anesthesia.

is, of course, only applicable to reversible states. The second approach to the treatment of lymphedema and elephantiasis is "excisional" with removal of the brawny, indurated areas and recovering of the underlying penis and scrotal contents with normal skin flaps or grafts. The excisional method is required when irreversible lymphedema or elephantiasis is present.

Larrey, in 1803, is credited with the first report of excision of a scrotal mass.[12] In 1820, Delpech wrote in detail of radical excision of scrotal elephantiasis, and this case report will be given in detail below.[13] Following these early cases, there have been numerous reports of removal of scrotal masses by Matas, Manson, Young, Davis, DeSavitsch, Finkle, Scardino and Prince, to name only a few.[14] The methods of excision varied little from the original reports of Delpech, and all consisted of a radical removal

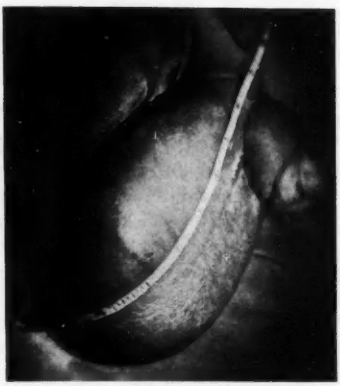


FIG. 3. Case 2. Preoperative view

of all diseased tissue and secondary coverage either by split-thickness grafts or by flaps of skin from adjoining areas. Many authors, particularly those with considerable experience, stress the fact that excision of tissue must be ruthless in order to prevent recurrence of swelling. Most failures reported occurred in those instances where removal of tissue was not radical enough. Poth, Macey, Blocker, and Gibson and Tough have reported the possibility of using the removed skin from the specimen as a split-thickness graft after completely separating it from the edematous

[12] Gibson, Thomas: Brit. J. Plast. Surg., **9:** 4–10, 1957.

[13] Delpech, J. M.: Chirurgie Clinique de Montpelier, 2nd vol. Paris and Montpelier: 1828.

[14] a) Matas, R.: Am. J. Trop. Dis., **1:** 60, 1913. b) Manson-Bahr, P. H.: Tropical Diseases. New York: Wm. Wood & Son Publ., 1921. c) Young, H. H. and Davis, D. M.: Young's Practice of Urology. Philadelphia: W. B. Saunders Co., 1926. d) Davis, D. M.: Ann. Surg., **92:** 400–404, 1930. e) DeSavitsch, E.: J. Urol., **45:** 216–222, 1941. f) Finkle, A. L., Scardino, P. L. and Prince, C. L.: A.M.A. Arch. Surg., **68:** 713–719, 1954.

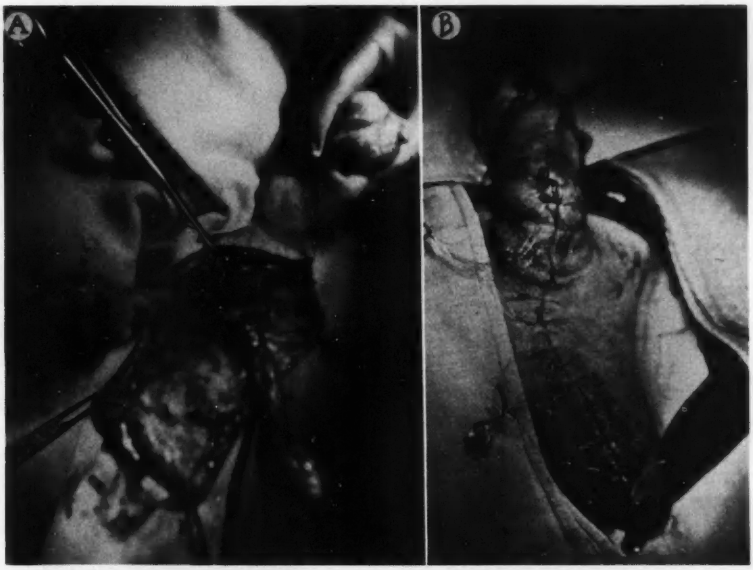


FIG. 4. Case 2. *A*, following excision of scrotal skin and edematous tissue. Penile revision has not been started. *B*, scrotal and penile revision completed. Pressure dressing is applied.

subcutaneous tissue.[15] This principle has not been generally applied to the surgery of scrotal lymphedema, since adequate skin can usually be obtained from the adjacent thigh or perineum without resorting to a free graft.

The "physiologic" approach is first credited to Handley who, in 1908, attempted to re-establish lymph drainage in the leg by implantation of sutures across the barrier between the superficial and deep lymphatics.[16] This principle was applied to the surgery of lymphedema of the lower extremities by Kondoleon and reported in 1912.[17] His idea was to create an opening in the deep fascia of the leg and allow lymph drainage to occur between the superficial and deep lymphatics. The Kondoleon principle was not applied to the treatment of scrotal lymphedema until 1923 when Orr reported one case treated by creating a skin bridge between the scrotum and the groin.[18] Livermore, in 1943, reported the unsuccessful use of this method in one patient who later required excision of edematous scrotal tissue.[19] Nesbit, in discussing this paper, sug-

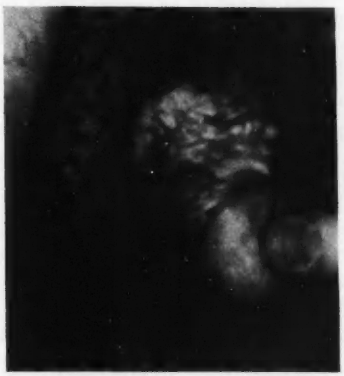


FIG. 5. Case 2. Three years following surgery. Scrotal result satisfactory. Further surgery necessary on penis.

[15] a) Poth, E. J., Barnes, S. R. and Ross, G. T.: Surg., Gynec. & Obst., **84:** 642, 1947. b) Macey, H. B.: J. Bone & Joint Surg., **30:** 399, 1948. c) Blocker, T. G.: Plast. & Reconstruct. Surg., **4:** 407, 1949. d) Gibson, T. and Tough, J. S.: Brit. J. Plast. Surg., **7:** 195, 1954.

[16] Handley, W. S.: Lancet, **1:** 783, 1908.

[17] a) Kondoleon, E.: Munch. med. Wochnschr. **1:** 525, 1912. b) Kondoleon, E.: Arch. Bel. de Chirurgie, Brussels, **27:** 103, 1914. c) Kondoleon, E.: Arch. Provincial de Chirurgie, **27:** 104, 1924.

[18] Orr, T. G.: Surg. Clin. North Amer., **3:** 15-37, 1923.

[19] a) Livermore, G. R.: J. Urol., **51:** 170–173, 1944. b) Livermore, G.: Trans. Am. Assn. Genito-Urin. Surg., **36:** 175–179, 1943.

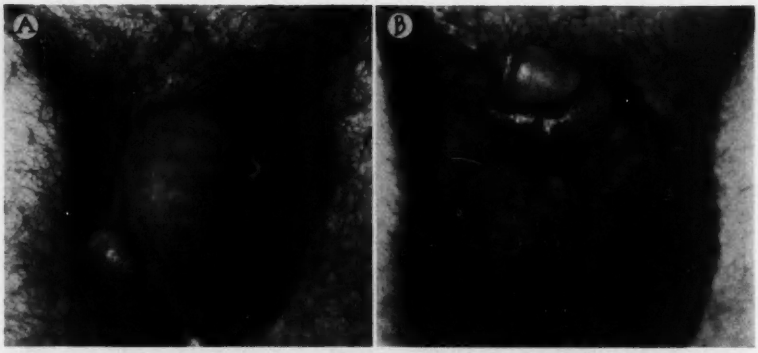


FIG. 6. Case 3. *A*, preoperative condition. Patient unable to void. Indwelling catheter necessary. *B*, 1 month after surgery. Patient able to void spontaneously.

gested that the Torek procedure might be applicable to the treatment of scrotal lymphedema. This would involve suturing the scrotum permanently to the thigh, as in the Torek orchiopexy, but with the hope of developing a new lymphatic drainage from the scrotum to the thigh. Moore, in 1937, also reported successful utilization of a similar procedure in one patient.[20] Huggins and McDonald, in 1950, reported 2 cases in which this principle was utilized, successfully.[21]

CASE REPORTS

Case 1 (figs. 1 and 2), is an historic case.[13] The patient was Jean Baptiste Autheir, who, in 1820, reported to the clinic of Prof. Jacques Mathieu Delpech in Montpellier, France. He gave a history of joining the horse militia at age 25, and, after 2 years in the service, of acquiring syphilis. He was treated with mercury inunctions, but re-joined the troops 3 months later with his penile lesion incompletely healed and with some inguinal lymphedema. In spite of this, he continued equitation for the next 7 years until he was completely disabled by the enormous swelling of his genitalia. At the age of 35, he was admitted to the hospital for surgery. The estimated weight of the scrotal mass was 60 pounds. On September 11, 1820, surgery was performed by Professor Delpech before 300 spectators in the amphitheater. No anesthesia was used, and several husky assistants were utilized to immobilize the patient. Skin flaps were first marked with ink and

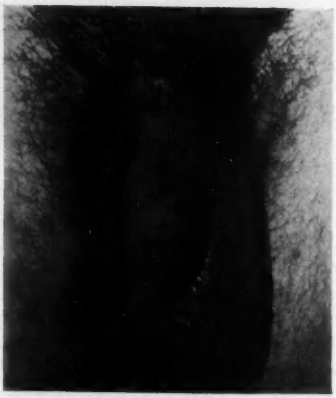


FIG. 7. Case 4. Preoperative view

dissection was carried out as depicted on the drawings. Fifty-seven minutes were needed for the initial dissection, and suturing was then carried out during the next half-hour. Postoperatively, the patient was described as being in shock for several hours. For the next 48 hours, blood-letting "was required to maintain his condition." There was moderate suppuration of "good quality" for several weeks. An inguinal abscess developed and drained on the fourth week, and following this healing was apparently uneventful. Because the patient was such a curiosity, he was kept in the hospital for five months and worked as an orderly. At the end of this time, he went A.W.O.L. and spent three weeks "drinking and practicing sexual excess." An autopsy performed following death showed a large liver abscess which apparently was the

[20] Moore, T.: Urol. & Cutan. Rev., **41:** 471–473, 1947.

[21] McDonald, D. F. and Huggins, C.: J. Urol., **63:** 187–190, 1950.

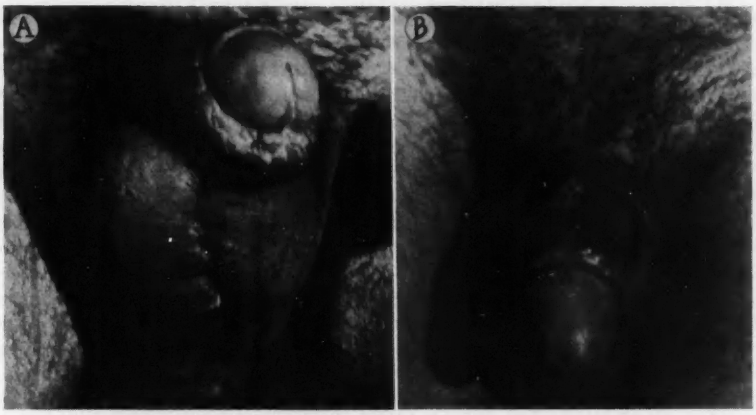


FIG. 8. Case 4. *A*, 2 months postoperatively. Some penile edema persists. *B*, fourteen months following first revision and 2 months following secondary penile surgery.

cause of his demise. The surgical result was excellent and functional for the short time of followup.

Case 2 (figs. 3, 4 and 5). A.F., Hosp. No. 482421, Chicago Wesley Memorial Hospital, Chicago, Ill., aged 40, a white man, was first seen on December 30, 1957 with scrotal enlargement 4 years in duration. He gave a past history of having an inguinal "buboe" at age 18. This required drainage twice. Fifteen years prior to the present admission he had considerable perirectal inflammation and pruritus ani. Physical examination upon entry was essentially negative with the exception of the finding of a healed inguinal incision on the left side. Laboratory work showed an essentially normal urinalysis and a normal blood count and differential. Blood smears for filaria were negative. In January 1958, 412 gm. of scrotal tissue was removed by excision with isolation and preservation of the testes and cords. Wire sutures and drain were utilized for closure. A separate penile incision on the dorsum of the penis was used for removal of skin from this area. The pathologic report of the removed tissue showed chronic granulomatous inflammation. Acid-fast smears and bacterial stains of the removed tissue were all negative. The patient re-entered the hospital in August of 1958 for penile revision. He was last seen on January 14, 1961 at which time the scrotum appeared to be of normal size with no brawny edema of the subcutaneous tissue. The penis still had several patchy areas of lymphedema, and was considerably crooked on erection. Further plastic repair of this area will be required, and the patient plans to have this done in the near future.

FIG. 9. Case 5. Preoperative view

Case 3 (fig. 6). J.E., Hosp. No. U - 9846, U.S.V.A. Research Hospital, Chicago, Ill., a 44-year-old white man, was seen following abdominal perineal resection for epidermoid carcinoma of the anus with extension to the right external iliac, femoral and peri-aortic nodes, all of which were removed by gland dissection at the time the initial surgery was performed. Tumor was known to be left in the hypogastric nodes. Extensive irradiation therapy was subsequently

administered to the lower pelvis followed by the development of edema 1 month after completion of therapy. Penile edema prevented spontaneous urination, and made necessary an indwelling Foley catheter for adequate bladder drainage. The patient requested surgery as a palliative measure in order to allow removal of the inlying catheter. The laboratory work was essentially non-contributory. On January 23, 1959, excision of the edematous penile skin was carried out by performing a dorsal slit followed by block dissection, extending down to Buck's fascia. The preservation of one broad-based flap of penile skin was possible and this was used to cover the penis. An indwelling catheter and pressure dressing were utilized for 1 week postoperatively. The pathology of the removed tissue showed lymphangiectasia and subepidermal fibrosis. Following removal of the catheter, the patient voided normally with no further difficulty until his death 1 year later from extensive carcinomatosis. The palliative result was deemed worthwhile, and the patient was very satisfied to be relieved of the troublesome catheter.

Case 4 (figs. 7 and 8). W.L., Hosp. No. U-11766, U.S.V.A. Research Hospital, Chicago, Ill., a 35-year-old white man, entered the hospital with a history of swelling of the penis and scrotum of 1 year's duration. At first, this was intermittent. There was some redness and tenderness of the genitalia accompanied by swollen lymph nodes. During the first part of his illness, the swelling was intermittent, but upon admission, it appeared to be a permanent lymphedema of the scrotum and penis. The past history revealed that he had lived in Tennessee for 11 years, had spent 4 years in the South Pacific during which time he had three attacks of malaria. Subsequently he spent 3 years in Korea. Examination of the abdomen revealed a palpable liver, enlarged 2 cm. below the costal margin. The penis measured 4 cm. in diameter, and the scrotum 18 cm. in diameter. Complete laboratory workup was carried out, including filaria and malaria smears, agglutination tests for typhoid, paratyphoid and Brucella; all of these were negative. Aspiration of material from an inguinal node showed no signs of acid-fast bacilli or fungi. On June 20, 1958, excision of the scrotal skin was carried out, together with a partial circumcision. The postoperative result was good as far as the scrotum was concerned, but 1 year later the patient had some remaining penile edema. A penile revision was done on June 5, 1959 and the postoperative result following this procedure was satisfactory. The pathology of the excised tissue on both occasions showed only acute and chronic inflammation of the skin and subcutaneous tissue with some lymphangiectasis. The end result was satisfactory and functional, according to the patient.

Case 5 (figs. 9 and 10). H.C., Hosp. No. 455657, Chicago Wesley Memorial Hospital, Chicago, Ill., a 49-year-old white man, was seen

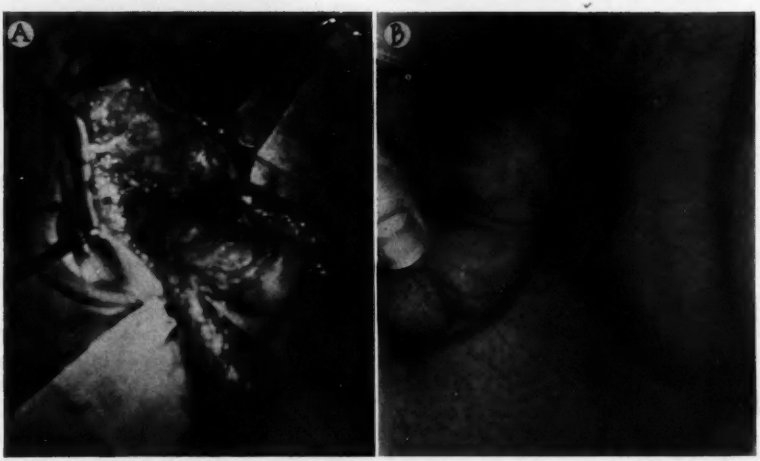


FIG. 10. Case 5. *A*, operative exposure just prior to closure. *B*, 2½ years following surgery. Scrotum essentially normal. Patch of lymphedema persists on dorsum of penis.

in 1957 with a history of scrotal swelling of 2 years' duration, accompanied by a purulent urethral discharge. The past history was noncontributory. Physical examination showed only localized edema of the scrotum and penis, as pictured. Laboratory studies showed 30 to 40 white blood cells in the urine and a positive urine culture for Streptococcus faecalis. The blood chemistry determinations and blood counts were all within normal limits. Multiple agglutinations for typhoid, paratyphoid, Brucella and smears for Filaria were all negative. Cystoscopic examination showed no pathological changes of the bladder and urethra; the urethral discharge subsided following antibiotic therapy. Surgery was performed on July 5, 1957 at which time most of the skin and subcutaneous tissue of the scrotum and base of the penis were removed. The pathologic study of the excised tissue showed acute and chronic inflammation of the skin and subcutaneous tissue without evidence of acid fast or filarial infection on smear. The patient was seen on March 28, 1961 at which time the scrotum looked excellent and postoperative result appeared to be satisfactory. There was still some patchy edema of the penis, particularly on the dorsum, but this did not interfere with erection or intercourse. The patient did not desire further surgery, and was well satisfied with the result.

DISCUSSION

Since the original report of radical excision of scrotal and penile lymphedema by Prof. Delpech in 1820, little has been added to the surgical therapy of this condition. Our experience bears out the warnings of previous authors that any surgery aimed at removal of such tissue must be radical and that subsequent procedures will frequently be necessary in order to achieve a satisfactory result. Two of our patients required more than one operation in order to remove all of the areas of lymphedema, and one patient still has several patchy areas which he does not wish to have removed. Creation of a new scrotum is not too difficult since any available adjacent skin of the perineum or thigh may be used to cover the testes and a satisfactory scrotal sac will usually develop in time. Free grafts have rarely been necessary in order to reconstruct the scrotum. The skin of the penis offers more of a problem, since scarring often interferes with satisfactory erection and intercourse. In this area, it is often necessary to utilize a split-thickness or free graft, and this procedure will probably be necessary in case 3 reported here.

We have had no experience with the physiologic approach, attempting to produce new lymph channels in the scrotum, and, in most instances, this would not seem to offer any advantage over the classic excisional approach. Excision certainly offers the quickest solution to the problem. Other types of surgery directed to restoration of lymphatic drainage lead to a higher percentage of failure, according to statistics in the literature. "Physiologic" operations require a longer convalescence, and leave the patient with an uncomfortable permanent skin bridge to the thigh. They frequently do not completely relieve the penile edema, although the scrotal swelling may be considerably softened. It is our opinion that excision of the diseased tissue certainly seems to offer the most direct approach to the problem with the highest chance of success.

SUMMARY

Four patients with penile and scrotal lymphedema were treated by excision of excess skin and subcutaneous tissue with satisfactory results. The surgical approach differs little from that described in a case report published 141 years ago.

Etiologic factors and a possible alternate approach to the surgical treatment of genital lymphedema are discussed.

251 E. Chicago Ave., Chicago 11, Ill.

DISCUSSION

Dr. John K. Ormond (Pontiac, Mich.): I am chiefly concerned to discuss Dr. Bulkley's paper in view of the experience that I have had in India and Africa. In India I had the opportunity to treat 4 cases of elephantiasis of the penis and the scrotum—not extreme cases. It is rather interesting to make the incision through the very thick white tissue under the hypertrophied skin and to come down to a normal penile shaft with the elastic tissues and fibers still intact. The difficulty comes when you try to excise all the skin because it extends up to the abdomen in a good many cases and out onto the thighs in others.

We were more concerned with the penis than we were with the scrotum because when you dissect the scrotum off, you find normal testicles, just as Dr. Bulkley showed in his pictures. You draw the skin together as much as you can from the thighs, and the scrotum will regenerate to a certain extent, although it still may show this chronic lymphedema. We were more concerned with restoring sexual powers to these men because nearly always elephantiasis develops in early life. The oldest one we saw was 35, and the youngest one was 16.

I can assure Dr. Bulkley that he doesn't need to worry about the results he will get with skin grafts. In these 4 cases that we did in India, we did split thickness skin grafts and got a perfect functional result sexually.

In Africa, I didn't see any of these; but they reported to me that there were a great many cases of elephantiasis of the female vulva, too. About all they could do was to lift it up, excise it, and repair it just by sutures.

I wanted to ask Dr. Leadbetter what objection there is to excising entirely a smaller stricture and merely repairing the urethra instead of resorting to a large operation, as he showed in his longer strictures.

I would like to ask Dr. Hamm if it is possible to operate on any of these valves perineally through a midline incision.

Dr. Edgar Burns (New Orleans, La.): I would like to direct my first remarks to Dr. Hamm's presentation. This first report of ours, that is, these figures that he showed of ours, is our first report of 81 cases in which we found three prostatic valves. At that time we were doing our diagnostic procedures by retrograde cystourethrography. Since that time we have a total of something over two hundred. In that group, Dr. Hamm, there have been six additional valves. Most of those have been found since you made that first report on voiding cystourethrograms.

We have found, just as I am sure all of you have, that a retrograde cystogram is adequate where you have marked dilatation; but it isn't adequate to pick up those that have less desiccation, and of course that is the state in which you would like to get to them. I am sure, from Dr. Hamm's reports and from the additional experience that we have had, as well as perhaps all of you here, that prostatic valves occur much more frequently than we have previously considered them to occur.

Insofar as treatment is concerned, we tried—certainly in the younger patients—an open procedure by separating the symphysis. But more recently, we have done it by transurethral resection, and it is certainly more satisfactory.

I would like to ask Dr. Leadbetter if he anticipates that hair will grow on the flap of scrotal skin he uses in doing that modification. I think all of us have had experience in having to take down the hypospadias in which repair has been done by the use of scrotal skin. We have recently done our third case where sometime previously, more than 20 years, the hypospadias repair had been made by a piece of scrotal skin. He had hair pulled off repeatedly because stones formed on it. It is an extremely unsatisfactory sort of procedure. In those cases we have simply taken it down and started over from scratch. I wonder if he may anticipate that hair may grow on this scrotal skin that he uses in the flap.

Lastly, in regard to Dr. Bulkley's presentation, we have had some experience with lymphedema of the scrotum and penis. We found that excision is a much more satisfactory procedure than trying to establish lymphatic drainage by the Torek approach.

Dr. Richard Chute (Boston, Mass.): I would like to ask Dr. Bulkley whether he gets recurrence eventually or what he finds after that.

Dr. Edward W. Campbell (Abington, Pa.): As many of you know, I have been intensely and actively interested in the urologic problem of the young since 1925. During that time we have had an opportunity of seeing a fairly large number of

these urethral strictures in children, both male and female. Of course, the great majority of them are strictures of the terminal urethra, especially the meatus.

QUESTION: What is it you call "it" in the female?

DR. CAMPBELL: The meatus.

QUESTION: You had another word once upon a time.

DR. CAMPBELL: As a matter of historical interest, 18 years ago I had the temerity to present before this Association a paper based on a reasonable-sized series of infants and children with congenital stenosis of the meatus. At the end of that paper I was publicly berated and demeaned, but not swayed or discouraged, by an old member who took me to task for deigning to present before this learned society such a lowly topic of apparent urologic insignificance. I made no rebuttal or excuse. If I had, I could have pointed out that several of the infants and children in that series had been seen and diagnostically overlooked by several of the older members of the urologic profession in New York, including some of the professors and some of whom were members of this Association in attendance.

I think we have come a long way since that time as evidenced by the program we have heard this morning and the programs we are hearing in our various sectional and national meetings.

I would like to show one slide so you can see what I have been talking about. This happens to be a slide I showed 18 years ago of an 18-month-old boy with congenital stenosis of the external meatus; bladder, 500 cc capacity; and quite a severely dilated and damaged upper urinary tract. (Slide) The only treatment necessary was meatotomy and persistent followup studies to make sure that there was no recontraction. During that period, there will be a revision of the upper urinary tract, a regression such as Dr. Hamm has shown.

In the diagnosis of stricture elsewhere in the urethra, I feel that the radiographs, shadowgraphs, are very good; but I like to look at them. For those who do not have the forward vision instruments small enough, I can suggest that you use a size 14 McCarthy sheath, in which you can use the adult-sized telescope and get a real picture of the stricture, of congenital valves, or hypertrophy of the verumontanum, or contraction of the bladder neck or anything else you want to see. I am surprised that a number of people are still trying to see these lesions with a right oblique telescope.

Regarding Dr. Bulkley's paper, I was very much interested because in the last 18 months I have been through an ordeal with a man by now 66. He is very heavy. For some reason or another, about three years previously he had a repair of the penile hypospadias carried out. Why he had it done at that late date I don't know. But anyway, he ended up with some complications. He had to have a suprapubic tube inserted. Scrotal and penile edema developed. The scrotum was about the size of a Persian melon, and the penis was the size of a great big sausage, 2¼ inches in diameter but greatly foreshortened.

His great complaint was that he lost his penis. Most of the time he couldn't find it. He couldn't get it out.

Well, he was large and had an overhanging pendulous abdomen. He had a ring of scar around the base of this penis.

I attempted to help him by excising the ring of scar. I removed about 25 pounds of fat by lipectomy and took off about three-fourths of his scrotum, leaving his testicles.

He did fairly well for about 4 months. Then the elephantiasis recurred. At that time I turned him over to a plastic surgeon. Now they are reconstructive surgeons. Dr. Chet Snyder down in Miami, who is excellent, completely denuded the penis. He cut his scrotum way back practically to the perineum. He took off both his testes, repaired bilateral inguinal hernias, and got an excellent result for about three or four weeks.

Then the fellow started to get big again. Then we woke up to the fact that he had a severe complicating monilial infection of the thigh and scrotum. We cleaned him up with an appropriate gel. All the edema disappeared. As of now he has a fairly respectable penis and scrotum.

The penis was the bare penis. It was covered with a split thickness skin from the lateral thigh, a piece of skin about four by seven. It made an excellent cosmetic result, but we didn't realize until too late that it was his monilial infection in the groin that was the important factor in the failure.

DR. DAVID M. DAVIS (Haverford, Pa.): In connection with Dr. Hamm's excellent paper, I would like to state that I saw a case of urethral valves in a female, age 16, who had complete retention of urine. The proximal half of the urethra was very widely dilated. It was impos-

sible to see these valves because of the inflammation present. But we assumed that they must be there because of the rest of the situation. We removed them with an old-fashioned Young punch with a spectacular result. The patient became perfectly well in a few days.

I would like to inquire of Dr. Nesbit whether these cells showed in the clear cytoplasm any lipoid material such as one finds in prostatic epithelial cells.

In regard to Dr. Bulkley's paper, I recall very well one of Dr. Young's cases in which the penis was about two inches in diameter. He did a complete removal, and the result was really very good. He was very proud of it. Just before the patient left, he inquired of the patient's wife what she thought of the result. She said, "Well, Dr. Young, it's beautiful; but I'm afraid that now you'll have to operate on me." [Laughter]

In regard to the covering, I recall another case where I had to denude the penis entirely for another reason in the case of an extensive extravasation of urine with necrosis. This was in a very black colored man. I covered the shaft of the penis with pinch grafts. I placed them very accurately in straight rows. They all took. As healing occurred, the pinch grafts joined up with one another so that the central part of each pinch graft was black and the spaces in between were white. It was very beautiful, like a checkerboard. [Laughter] Far from being a disadvantage, the patient was immensely proud of it. [Laughter]

QUESTION: May I ask a couple of questions? I would like to ask Dr. Leadbetter about diversion. He may have referred to it, but I didn't hear it.

I would like to ask Dr. Hamm if he does anything to this indentation at the bladder neck. I can see where that would be obstructing in itself even if secondary to his valve.

DR. WYLAND F. LEADBETTER (Boston, Mass.): To answer Dr. Ormond's question about resection and reanastomosis, I think certainly this may well be possible. I think the difficulty is that usually the anastomosis is circular. In a circular type of anastomosis, recurrent stricture, I think, would more often result.

This really is not a big procedure. It is a simple one. The suture is small. It takes very little time and really is not difficult to do. As I mentioned, our results have been quite satisfactory.

So far as the hair is concerned in the scrotum, I am sure this may be a problem. I think in at least one of the cases where we have had hair, the hair has gradually disappeared by itself. I can't explain this, but it has gone.

The other thing you can do with the hair is to perform fulguration with a shellac needle where the tip is just allowed to go into the root of the hair so that you don't destroy the skin, just the hair follicle.

Inasfar as diversion is concerned with these patients, we have not used diversion as yet. I am sure in some cases where infection of the urine is present that either a suprapubic tube temporarily or urethrotomy would be indicated.

QUESTION: You don't leave in a urethral catheter?

DR. LEADBETTER: Yes. We do place a urethral catheter in the first stage for about three days and then remove it. In the second stage the urethral catheter has been left in six to seven days. This is removed, and the patient is allowed to go.

DR. FRANK C. HAMM (Brooklyn, N. Y.): Dr. Ormond inquired about the repair of these valves through a perineal approach. We have not used that, but it has been described. Of course, the resectoscope in the newborn is introduced through an external urethrotomy. I perhaps didn't mention that.

I want to thank Dr. Burns for his kind remarks; and, of course, Dr. Campbell; I really didn't give him the credit he deserves for all this work because this is not original with us by any means. He used all of these modalities years ago and showed the way for the whole thing, actually.

I want to thank Dr. Davis for his kind remarks.

Dr. Spence inquired about the removal of the secondary obstruction of the bladder neck. That is a problem. I don't know how often one has to deal with it. We had to revise that on one of our patients.

But I think it is worthwhile to do your valve first. I think that the detrusor will take care of itself in most instances.

DR. GEORGE J. BULKLEY (Chicago, Ill.): In answer to Dr. Chute's question about recurrence rate, apparently this is not a serious problem. The reports have very few followup studies, but those that are available do not mention any recurrence. It would seem logical that over a period of time there certainly would be some. We have not had long enough experience to make any statement.

THREE ATYPICAL CHROMATIN-POSITIVE MALE PATIENTS

R. G. BUNGE AND J. T. BRADBURY, Sc.D.

From the Departments of Urology and Obstetrics and Gynecology, College of Medicine, State University of Iowa, Iowa City, Iowa

The Klinefelter syndrome, first described by Klinefelter, Reifenstein and Albright in 1942, was considered a post-puberal syndrome. Several significant observations made since the original description include the presence of chromatin bodies in somatic cells of these individuals, their chromosomal constitutions, the low incidence of color blindness (as in genetic females), the possible detection of prepuberal boys who will develop the syndrome, and the likelihood that the syndrome may represent a true intersex.[1]

Our first case, while representative of Klinefelder's syndrome, did present some unusual clinical signs. The patient was bald, had abundant facial and body hair and the pubic escutcheon was of the male type, in contrast to the "furcap" hairline, scanty beard and body hair and female type of escutcheon usually associated with the disorder.

CASE REPORTS

Case 1. J. J., a 32-year-old white man, complained of infertility after 2½ years of marriage. The history revealed no significant antecedent episodes which could have related to his problem. He shaved daily, was able to carry on his work in a crate factory and had normal marital activities.

Physical examination revealed a balding, well-nourished, and developed man: height, 176.5 cm.; span, 179 cm. The beard was moderately developed. Black hair was present on the chest and abdomen and arranged as a male type of escutcheon in the pubic area. The male-type breasts were present. The penis measured 7 cm. in length and each testis in the scrotum measured 2 by 2 by 1.5 cm. The prostatic gland was slightly enlarged and felt benign (fig. 1). Laboratory examinations: Routine blood and urinalyses were within normal ranges. A semen sample was devoid of spermatozoa. A buccal smear revealed that 58 per cent of the cells contained a single chromatin mass. Urinary gonadotrophins were moderately elevated.

Biopsies of the testes revealed characteristic histologic findings. There were adenomatous masses of interstitial cells, many hyalinized seminiferous tubules, and isolated tubules containing sustentacular cells only (fig. 2). In one section a seminiferous tubule contained germinal cells with partial spermiogenesis. This was consistent with the histologic picture of a chromatin-positive Klinefelter testis.

All published reports of Klinefelter syndrome known to us indicate a presence of bilateral small scrotal testes.

Case 2. D. J., a 17-year-old white man, was referred from the medical service for advice because of an undescended left testis. At the age of 9 years, a series of hormone injections had failed to induce descent.

Medical complaints were obesity and asthma, the latter arising from an allergy to dust, the former associated with nervousness and a desire to eat all of the time during the past 10 years. Nocturnal enuresis had occurred all of his life except during the month prior to consultation when his food intake was limited to 1,000 calories per day.

The patient was an obese white youth and dull mentally. Weight, 106 kg.; height, 180 cm.; span, 178 cm.; pubic to heel measurement, 100 cm. (fig. 3). Some acne was present on the face and the beard was scanty; gynecomastia was not demonstrated. The pubic hair was of female configuration. The penis was 4.5 cm. in length. The right testis was soft, measured 1 by 5 by 1.0 by 1.0 cm. and was in the scrotum. There was a soft, indistinct, small mass of tissue in the left scrotum. Bilaterally, both ducti deferentia could be palpated.

Laboratory examinations: Routine blood and urine examinations were within normal ranges. A 24-hour collection of urine contained 12.8 mg. 17-ketosteroids with 4.8 mg. 17-ketosteroids per gram of creatinine. Urinary gonadotrophins were moderately elevated. The oral mucosal smear revealed that 48 per cent of the cells contained a single chromatin mass. Excretory urograms were interpreted as normal.

A biopsy was taken from the right testis, then the left inguinal region explored surgically. The

[1] Bunge, R. G. and Bradbury, J. T.: The Klinefelter syndrome. J. Iowa State Med. Soc., **51**: 217, 1961.

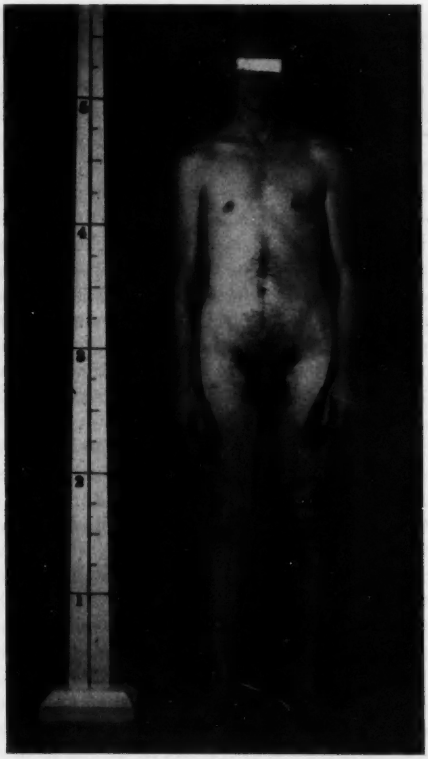


FIG. 1. Case 1. Note baldness, abundant body hair, male escutcheon, and lack of breast enlargement. Chromatin test was positive.

left ductus deferens and pampiniform plexus were easily identified distal to the external ring and appeared to end in a mass of coiled tissue, from which a biopsy was taken. A search made for a gonad in the region of the internal inguinal ring was futile.

Microscopic findings: The material from the right testis showed hyalinized seminiferous tubules, occasional tubules which contained only sustentacular cells, and an increased number of interstitial cells for the most part appearing in clumps adjacent to the larger seminiferous tubules containing cells. The cytoplasm was granular and dark staining, and often appeared in the paranuclear area as a clump while the rest of the cytoplasmic area was relatively clear. Serial sections revealed the presence of an intratubular body in some respects similar to the one described in the testes of a 10-year-old boy whose chromatin test was positive. We had never seen this type of body in biopsies of testes from adult patients with chromatin positive Klinefelter syndrome (fig. 4, *A*).

The material from the left scrotum appeared microscopically as a coiled tubule within a fibromuscular stroma. The epithelium was of the columnar type and was thrown into folds. It was interpreted as epididymis. No gonadal tissue was present (fig. 4, *B*).

The third case was most unusual in that Klinefelter's syndrome was the first clinical impression and that the final diagnosis was of true intersex.

Case 3. D. H., a 24-year-old white man, was first seen in 1952 for recurrent pain in the right lower quadrant of the abdomen which originated whenever pressure was applied to the right inguinal region (fig. 5). The patient had been born with an undescended right testis and perineal hypospadias. At another clinic, surgical correction of the latter was performed in stages. In 1941 an abdominal exploration revealed no evidence of uterus, tubes or ovaries. Two small nodules in the inguinal regions were identified as testes "by palpation of the vas deferens extending from each." In 1951 a right orchiopexy was performed and the surgeon described the conditions as follows: "The right testicle lay at the external ring. It was about twice normal size. When opened, it was bluish in color and hemorrhage had occurred into the hemorrhagic cystic cavity about 2 cm. in diameter. There was a second cavity about 1 cm. in diameter. Tissue from the right testicle showed fibrous tissue."

Physical examination revealed a slightly obese patient, whose musculature was flabby. Height, 151 cm.; span, 149.8 cm. There was some webbing of the neck. Breasts were of the male type. The pubic escutcheon was of the female type. The penis was small and showed the effects of surgical repair of hypospadias. The right testis could be palpated at the level of the external ring and was painful to pressure. The left testis in the scrotum was described as atrophic. The prostate gland felt normal on rectal palpation.

Laboratory findings: Routine blood studies and urinalysis were within normal ranges. A buccal smear showed that 52 per cent of the cells contained a single chromatin body. A 24-hour urine collection contained 10.0 mg. 17-ketosteroids per gram of creatinine. Urinary gonadotrophins were at castrate levels.

Removal of the painful right testis was recommended. At operation the right testis measuring

FIG. 2. Case 1. Photomicrograph of material from testis. Note adenomatous masses of interstitial cells, hyalinized seminiferous tubules, and seminiferous tubule with Sertoli cells in left center.

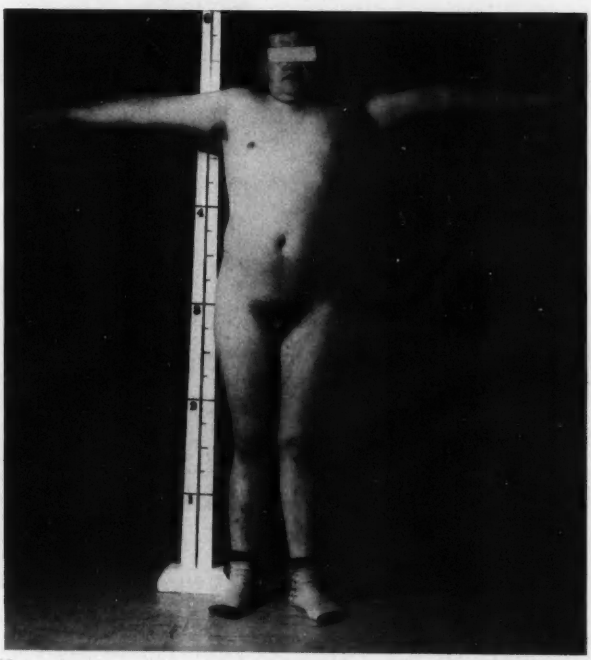


FIG. 3. Case 2. Note obesity and female pubic escutcheon. Chromatin test was positive.

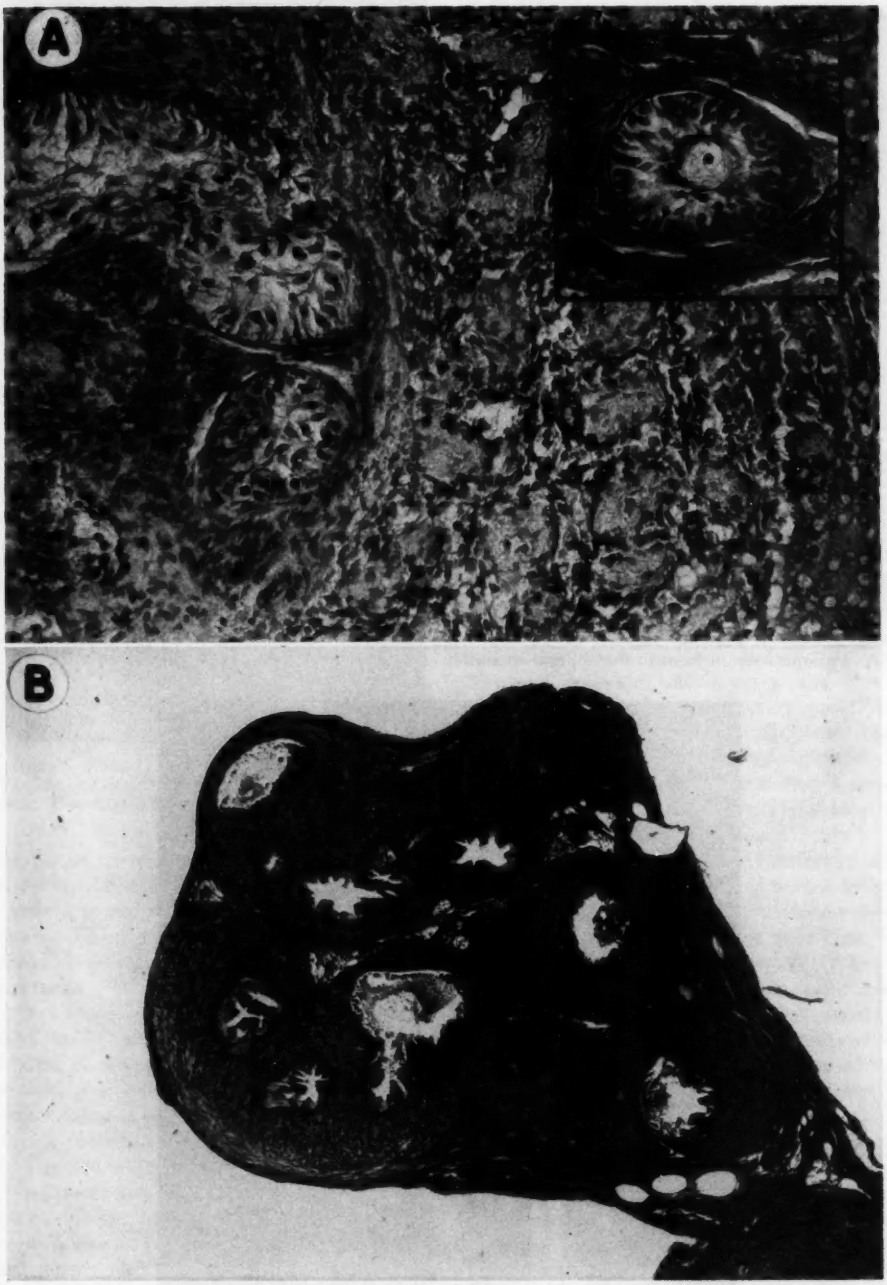


FIG. 4. Case 2. Photomicrographs. *A*, specimen from right testis shows hyalinized seminiferous tubules, some tubules with Sertoli cells between which are seen many interstitial cells. Insert depicts intratubular body described in text. *B*, coiled structure found in left scrotum and interpreted as epididymis. No gonadal structure found.

FIG. 5. Case 3. Note rather large head, webbed neck and female escutcheon. Chromatin test positive.

2.5 by 2.5 by 2.0 cm. was found at the external inguinal ring. An epididymis and vas deferens were identified. These structures and the testis were then removed. The left scrotum was opened and a biopsy obtained from the small testis.

Microscopic findings: The right testis presented several histologic characteristics found in the testes of patients with chromatin-positive Klinefelter syndrome. The interstitial cells were numerous and in adenomatous groups. The cytoplasm of some of these cells was granular and contained brownish pigment. No Rienecke crystals were seen. Hyalinized seminiferous tubules were abundant; however, a rare tubule with sustentacular cells could be found. One feature which we have not noted in testicular tissue from chromatin-positive Klinefelter patients was the presence of empty tubules (30–40 mm. in diameter). At times laminated calcific bodies almost filled the lumens and appeared to be attached to the wall of the tubule by a stalk-like structure. In one section, a small but similar body occupied the center of a seminiferous tubule which contained sustentacular cells (fig. 6).

The left gonadal material at low power showed a dark staining periphery and a light staining interior. The outer area was composed of adenomatous interstitial cells, hyalinized seminiferous tubules and occasional spindle shaped cells (fig. 7). A thorough search of the available sections showed a definite corpus fibrosum and, in one section, an oocyte within a primitive follicle was found (fig. 8). The left gonad was designated as an ovotestis rather than testis.

DISCUSSION

The Klinefelter syndrome as first described was thought to represent post-puberal sclerosis of the testes. However, there is little doubt that the disorder is of congenital origin particularly when recent observations of low incidence of color-blindness, of prepuberal chromatin-positive boys whose testes present histologic findings wholly unlike those of patients with the syndrome, and observation that such patients have an XXY chromosomal constitution. Further support of the congenital origin is offered in the reports that many of these patients are of low mentality and that mongolism may be a prominent feature of the disease. The authors have carried the interpretation a bit further in the past, by suggesting that the Klinefelter syndrome is an adult manifestation of true intersex. The evidence for true intersexuality is found in the XXY chromosomal constitution, the presence of chromatin bodies in somatic nuclei, and the intratubular bodies found in the testes of prepuberal chromatin-positive boys which have a striking resemblance to intratubular oocytes described by the authors in a human ovotestis. These 3 cases have been presented as additional evidence of the congenital nature of the disorder and the possibility of true intersexuality.

The first patient was unusual in being bald, having a moderately developed beard and a male type of pubic escutcheon in contrast to the usual "furcap" hair line, scanty facial and body hair and female pubic escutcheon. The testicular histology was, however, typically that seen in the syndrome.

The second case was unusual for its unilateral anorchia. The syndrome as defined speaks of small testes and if one wished to be a dogmatist this patient should not be considered as an example of Klinefelter syndrome. There is, however, some evidence that both testes were present at some time in the past since there was a persistence of the epididymis and ductus deferens (wolffian structures) bilaterally. Their differentiation, according to the Jost theory, must have been due

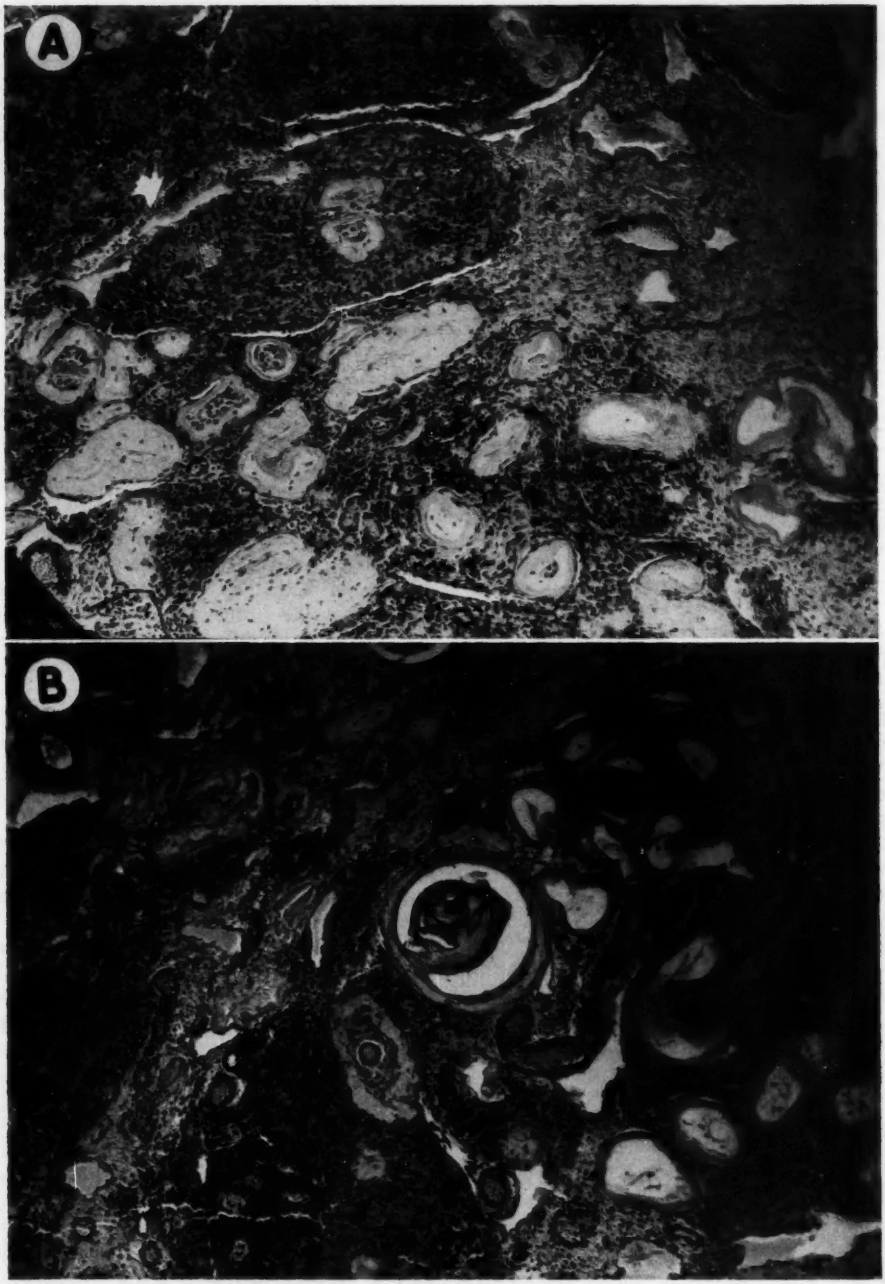


FIG. 6. Case 3. Photomicrographs. *A*, note many hyalinized tubules, some of which contain sustentacular cells, also adenomatous groups of interstitial cells. *B*, another section of right testis shows group of tubules containing few spindle cells. Larger center tubules contain calcific laminated body attached by stalk to wall. Just below and to left, smaller, similar body is within seminiferous tubule.

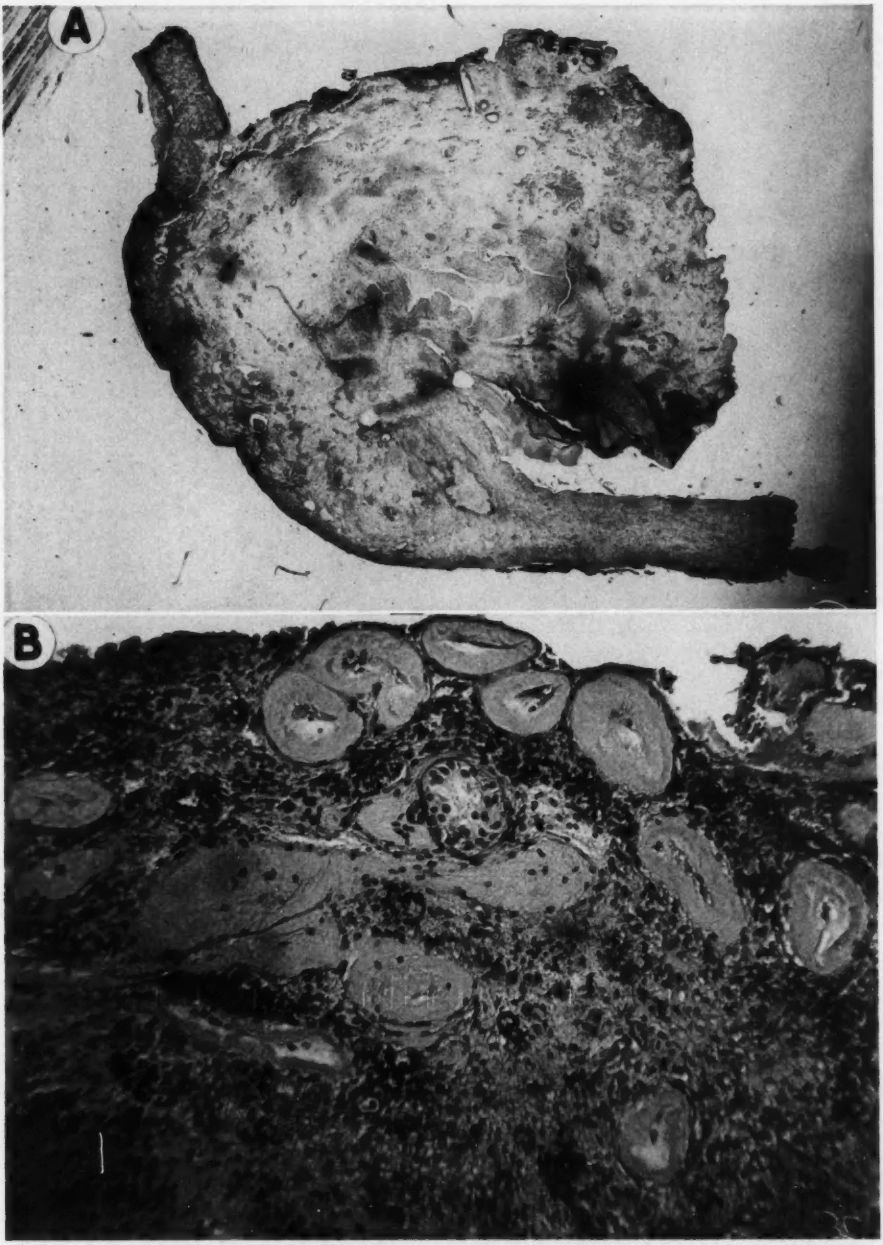


FIG. 7. Case 3. Photomicrographs. *A*, left ovotestis, low power. Note dark areas at periphery composed of interstitial cells and hyalinized seminiferous tubules. Note distinct corpus fibrosum in low center. *B*, peripheral edge shows interstitial cells, hyalinized seminiferous tubules and tubule with sustentacular cells.

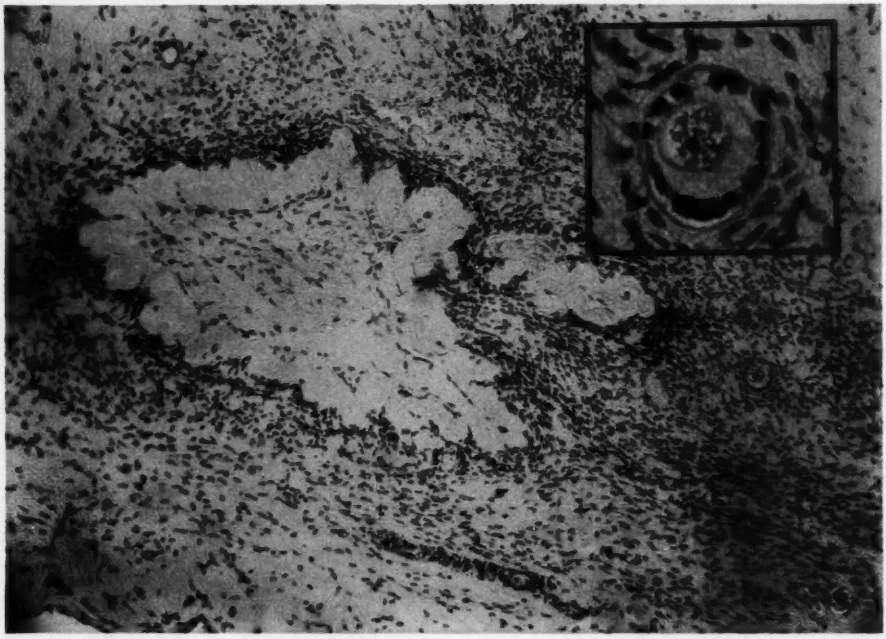


FIG. 8. Case 3. Higher power magnification of corpus fibrosum seen in figure 7. Follicle with oocyte is right center. Insert is photomicrograph of follicle.

to the presence of a testicular evocator and this was then followed by disappearance of one testis. One other feature of this case was the intratubular body in the remaining testis. Although the microscopic picture of adenomatous Leydig cells, ghost tubules, etc., was typical for the Klinefelter testis we have not seen such an intratubular body in any other adult Klinefelter testicular biopsy. There exists the possibility that a chromatin-positive man or boy with bilateral anorchia will be found.*

The third case was of special interest because of its multiple genital anomalies, wrong clinical impression and unique histologic findings in the gonads. Had a biopsy been obtained of only the right testis, the chromatin-positive nature of the somatic nuclei and typical testicular findings would have substantiated a diagnosis of Klinefelter syndrome. However, this impression had to be discarded when examination of the left gonadal material indicated ovotestis. Several cases reported as true intersexes have had rather typical "Klinefelter testes." Berardenelli[2] described a case in which there was an abdominal ovary and a scrotal testis. A biopsy was obtained from the latter and its histology was typical of sclerotic tubules of the Klinefelter testis. The patient was thought to be an example of the syndrome until an ovary was found at laparotomy and the case classified as hermaphroditismus verus lateralis. Armstrong, Gray, Race and Thompson[3] reported a case of true intersex in which the testicular histology was that of the Klinefelter testis. Our own case is similar, an ovotestis and the other gonad a testis with Klinefelter histologic findings. This evidence suggests that the Klinefelter syndrome is an adult manifestation of true intersexuality or that the syndrome and true intersexuality have a quite similar genetic etiologic background.

One final point is worthy of consideration. We are less inclined to rely on clinical signs when attempting to establish a differential diagnosis in male patients who have small testes. All such cases should have a chromatin test and biopsies obtained from all gonadal tissue in order to establish a firm diagnosis.

* A Personal communication from Dr. Edgar Burns describes such a case.

[2] Berardinelli, W.: Hermaphroditimus versus lateralis. Acta Endocrinol., **9**: 297, 1952.

[3] Armstrong, C. N., Gray, J. E., Race, R. R. and Thompson, R. B.: Case of true hermaphroditism; further report. Brit. Med. J., **2**: 605, 1957.

RENAL LEUKOPLAKIA: OBSERVATIONS OF BEHAVIOR

BAXTER A. SMITH, JR., EDGAR A. WEBB AND WILLIAM E. PRICE

Leukoplakia of the renal pelvis, sometimes referred to as renal cholesteatoma, is an uncommon disease, poorly understood as to its natural history and unsatisfactory as to its treatment. It has been recognized since 1882 but our knowledge of this serious condition is still meager. The diagnosis has seldom been made clinically, conservative treatment has been rare, and followup reports have been short.

Leukoplakia is a metaplasia of the transitional epithelium of the urinary tract but should more properly be referred to as dysplasia or dyskeratosis. Transitional epithelium is of ento- and mesodermal origin in the bladder and of mesodermal origin only in the ureter, pelvis, and ducts of Bellini. The same metaplasias occur in both areas. Thompson and Stein[1] proposed the concept that transitional epithelium is in reality modified squamous epithelium. It is interesting to note that glandular mucosa is the normal in the ureter of the horse.[2]

When metaplasia proceeds towards the squamous side with cornification, leukoplakia is present. This is not to be confused with the common squamous metaplasia of the trigone in the female patient, varying with the hormonal cycle. The dysplasia may progress to malignancy in which event it is of squamous type with its foreboding portent.

Leukoplakia of the renal pelvis is a disease of middle age. Sexes are affected alike. Approximately 110 cases have been reported and of these, 90 per cent were unilateral. About 15 cases have had a preoperative diagnosis. Five cases have been treated conservatively in recent years. As a result, most of our knowledge of its behavior is by history rather than observation.

Etiology is vague but seems to be an individual response to irritation, almost always of, or associated with, infection. Although it is possible that it is primary metaplasia with secondary infection, large autopsy series should disprove this. Potts[3] found no squamous epithelium in 354 sections of 26 urinary tracts but Connery[4] found squamous epithelium in 8 per cent of bladders routinely sectioned at autopsy. Stone is frequent but often represents deposition of salts on a keratin nidus with urea-splitting infection, though stone is often known to be present long before the clinical picture of leukoplakia appears. If an irritant is excreted in the urine, one would anticipate more generalized involvement but perhaps it is like urothelial tumor. Reversal of the process following urinary diversion has been reported. This did not occur in case 7. There is much opinion that the process is not reversible. However, it is no doubt reversible if the irritant can be removed and the process is not too well established.

Microscopic pathology is well known but the presence of areas denuded of mucosa presenting the appearance of granulation tissue has not been emphasized. This is mentioned seven times[5-11] in pathologic descriptions but no doubt is frequently deleted in reports or overlooked by pathologists. In six of our patients who had eight partial nephrectomies, this was present in all and in some, no mucosa could be found on study of numerous sections. Leukoplakia may be in scattered patches or in large confluent areas. It may involve mucosa from the external meatus to the calyces. In the cases reported by Naumann and Sabatini[12] and by Armstrong, Harlin, and Fort[10] there was involvement of the collecting tubules;

[1] Thompson, G. J. and Stein, J. J.: Leukoplakia of the bladder. J. Urol., **44:** 639–649, 1940.

[2] Johnson, F. R.: Some proliferative and metaplastic changes in transitional epithelium. Brit. J. Urol., **29:** 112–120, 1957.

[3] Potts, W. J.: Squamous cell carcinoma of the renal pelvis associated with stone and leukoplakia. Arch. Surg., **25:** 458–466, 1932.

[4] Connery, D. B.: Leukoplakia of the urinary bladder and its association with carcinoma. J. Urol., **69:** 121–127, 1953.

[5] Küttner, H.: Das Cholesteatom der Harnwege. Beit. klin. Chir., **114:** 609–641, 1919.

[6] Rona: Quoted by Küttner.

[7] Hinman, F., Kutzmann, A. A. and Gibson, T. E.: Leucoplakia of the renal pelvis. Surg., Gynec. & Obst., **39:** 472–489, 1924.

[8] Kutzmann, A. A.: Squamous cell carcinoma of the renal pelvis with special consideration as to etiology. J. Urol., **39:** 487–505, 1938.

[9] Richey, D. G.: Leukoplakia of the pelvis of the kidney: A study in metaplasia. J. Lab. & Clin. Med., **5:** 635–639, 1920.

[10] Armstrong, C. P., Jr., Harlin, H. C. and Fort, L. A.: Leukoplakia of the renal pelvis. J. Urol., **63:** 208–213, 1950.

[11] Baron, C.: Leukoplakia of the renal pelvis. J. Urol., **73:** 941–944, 1955.

[12] Naumann, H. N. and Sabatini, S. A.: Cholesteatoma of kidney simulating squamous cell carcinoma. J. Urol., **69:** 467–473, 1953.

these were probably "sponge" kidneys by description. If keratin has been desquamated, the squamous epithelium may not appear grossly different from transitional epithelium. Although the affected area may appear limited, the potential is diffuse.

Metaplasia and dysplasia have intrigued the urologist and pathologist for many years. Their thorough consideration is beyond the scope of this paper. More recently, the respiratory tree has come to the forefront where squamous metaplasia merges to carcinoma in a single microscopic field. The now frequent cold cones of the cervix show normal squamous epithelium, dysplasia, and carcinoma side by side. With the exception of Thompson and Stein and of Shabad,[13] most observers are convinced that metaplasia, particularly squamous, of the urinary tract is associated with a high incidence of carcinoma. Connery found that carcinoma developed in 20 per cent of 45 patients with vesical leukoplakia. Shabad believes that metaplasia from transitional to squamous epithelium differs from that of normal squamous epithelium to leukoplakia. Most of the experimental production of metaplasia has been produced in the respiratory tract (evil tobacco).

Keratin is a rather insoluble, indigestible, inert scleroprotein containing cystine and methionine in various linkages of straight polypeptide chains. Various kinds of keratin make up skin, callus, hair (wool), and horn and hoof. Papain is reported to digest keratin and a digestive enzyme of the larva of the clothes moth digests the keratin of wool very well.[14] Some of the keratins can be altered chemically ("stretch" wool, permanent waving) and perhaps we could get leads from the chemists in the tanning, wool, or cosmetic industries. If irrigations could be utilized to digest and disrupt the major portion of a keratin (cholesteatomatous) mass, multiple operations might be avoided.

Symptoms are those of chronic infection, usually with vesical irritation, and recurrent episodes of renal colic often accompanied by fever and chills. It is common to find that the history goes back 10 to 20 years. The patient may have become an addict. Pyuria may be absent between episodes of colic early in the course of the disease, and the original culture occasionally may be sterile. A history of hematuria is noted in about one-third of the cases.

Passage of sheets of desquamated squamous epithelial cells is diagnostic. Direct questioning is sometimes required to elicit a proper story but the patient usually volunteers that he has passed pieces of skin, gritty flakes, soft stones, white chunks, or membrane or tissue in the urine. Rather massive quantities of desquamated material are passed at times (fig. 1, *D*). Baselin's[15] patient passed 1 kg. keratin during 200 attacks of colic in 5 years. These masses look like a spit ball, putty, or like wet toilet tissue. Because of the latter appearance, nurses tend to discard the results of straining the urine during and after attacks of colic, especially when the patient is female. When confronted with this behavior, the nurse usually responds nonchalantly, "I thought you were looking for stones." Despite this characteristic finding, only about 15 reported cases have been diagnosed preoperatively. Scattered squamous epithelial cells in the bladder urine of the female should not be considered significant.

If there is leukoplakia of the bladder, one suspects the same cause for upper tract symptoms. When the bladder is uninvolved, one may see particles of epithelium and keratin floating in the bladder, usually at first thought to be purulent shreds. An observer cannot help but transfer the vesical picture, readily observable, to the renal pelvis. Thompson and Stein present an excellent account of vesical appearance and behavior.

The radiologic appearance of renal leukoplakia is protean. Early, between episodes of obstruction, the pyeloureterogram may appear normal. If the plaque is thickening and the keratin is piling up, an incompletely filled pelvis will show irregularity and wrinkling. Stone is present in one-half of reported cases. Non-opaque (or faintly opaque) filling defects are seen when layers of keratin peel off and these may have a typical concentric arrangement giving the onion-skin, moth-eaten appearance often described. Calyces or segments may not fill. The picture of destruction by infection, eventually pyonephrosis, ensues. Ureteral involvement may present as irregularity in the ureteral wall but more commonly shows obstruction with filling defects and proximal dilatation. Usually the findings are associated with passage of desquamated wads from the renal pelvis.

In differential diagnosis, infection comes first

[13] Shabad, A. L.: Leucoplakia of the bladder. Problems of Oncology, **5**: 82–89, 1959.

[14] Rothman, S.: Physiology and Biochemistry of the Skin. Chicago: Univ. of Chicago Press, 1954, pp. 349–360.

[15] Beselin: Quoted by Küttner.

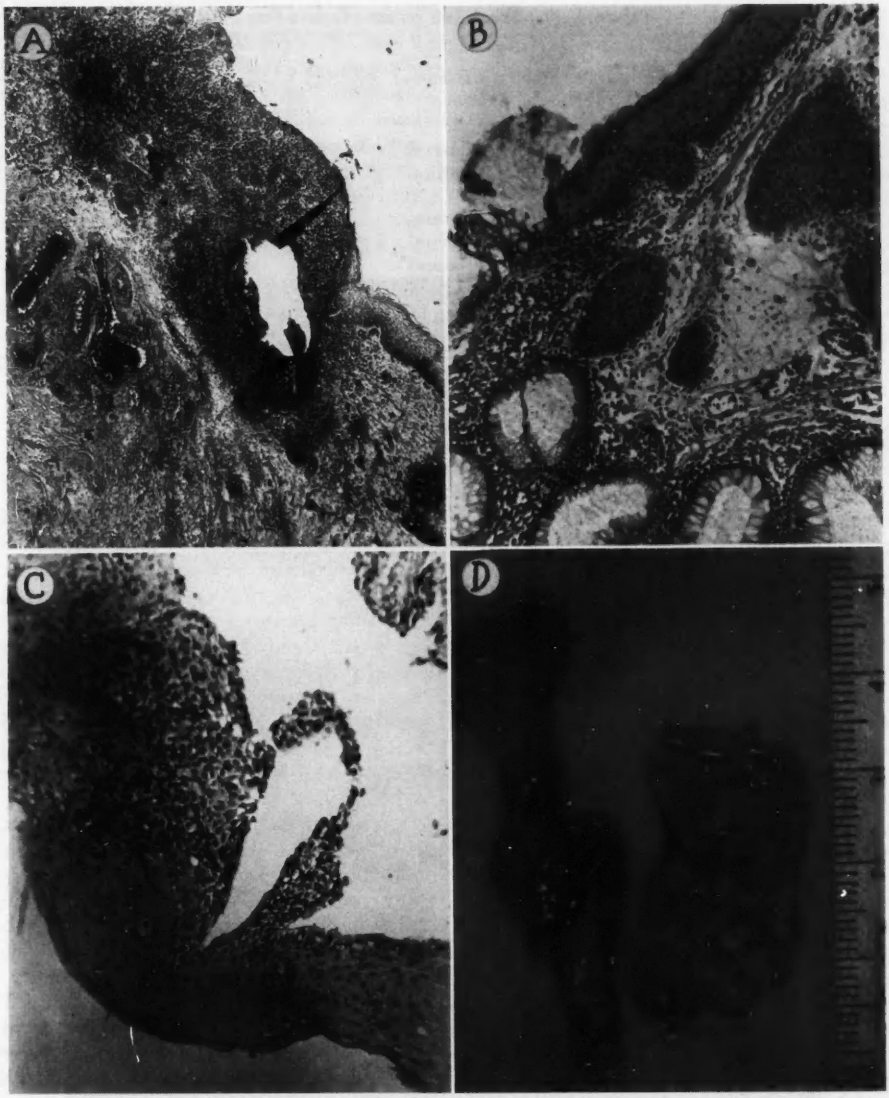


FIG. 1. *A*, case 1. Vesical biopsy demonstrates change from leukoplakia to carcinoma. Marked inflammation is present at transition zone.
B, case 3. Glandular and squamous metaplasia of bladder in same microscopic field.
C, case 4. Vesical biopsy demonstrates transition of leukoplakia to carcinoma.
D, case 2. Example of material passed.

and all stages up to eventual pyonephrosis enter into consideration. Leukoplakia should be kept in mind whenever one encounters chronic infection without obvious cause. Tuberculosis is commonly mimicked; Taylor[16] and Kutzmann[17] each found concomitant tuberculosis in one-sixth of their reviewed cases. One of our cases had acid-fast bacilli present upon stain of material in the renal pelvis but tissue examination revealed no findings to suggest tuberculosis, and cultures have been

[16] Taylor, W. N.: Leukoplakia of kidney pelvis and ureter. Am. J. Surg., **32**: 335–342, 1936.

[17] Kutzmann, A. A.: Leukoplakia of the renal pelvis. Arch. Surg., **19**: 871–897, 1929.

TABLE 1. *Statistical data on nine reported cases*

Patient	Sex	Age	Duration Symptoms Yrs.	Followed Yrs.	Side Involved	Bladder Involved	Stone		Total Procedures
							Initial	Subsequent	
1. C. K.*	M	42	22	13	bilateral	yes	yes(R)	yes(R)	19
2. D. E.	F	37	3	15	bilateral	no	yes(B)	no	14
3. G. S.	M	47	16	12	left	yes	yes(L)	yes(L)	16
4. M. A.	F	49	8	11	bilateral	yes	no	yes(B)	7
5. A. J.	F	48	20	10	bilateral	yes	no	yes(B)	21
6. P. C.*	M	39	10	5	bilateral	no	yes(B)	yes(B)	21
7. P. T.	M	45	18	4	bilateral	yes	no	yes(B)	7
8. I. F.	M	46	1	4	right	no	yes(R)	yes(R)	9
9. L. S.	M	27	1 wk.	2½	right	no	no	no	5
	5M 4F	42	11	9.5	6B 2R 1L	5	5	7	13

* Dead

negative. We are at a loss of evaluate this finding. Infiltrative carcinoma of urothelial origin must be considered. One-sixth of the cases of leukoplakia of the renal pelvis reviewed by Kutzmann, by Taylor, and by Patch[18] had squamous carcinoma. Utz and McDonald[19] found leukoplakia in four of 23 cases of squamous carcinoma of the renal pelvis. We have seen four instances of squamous carcinoma of the bladder in association with vesical leukoplakia. We have seen a patient with a small communicating hydatid cyst who gave a 10 year story of passage of "tapioca" and had pyelographic findings compatible with renal leukoplakia.

Treatment leaves much to be desired. Prevention would be ideal but until the nature of the irritant and factors influencing individual response are known, the best we can do is control infection and remove calculi, perhaps even silent ones. If the lesion is unilateral, nephrectomy is usually performed, even when preoperatively diagnosed, because of the prolonged recurrent morbidity and the malignant potential. However, one is reluctant to discard a relatively good kidney and bilaterality in six of our 9 cases makes us hesitate. Conservation demands a calculated risk.

In case of bilateral disease, preservation of parenchyma is essential. The recurrent episodes of obstructed infection due to passage of keratin progressively take their toll of nephrons with varying rapidity and should be relieved promptly. Adequate drainage is mandatory. Partial nephrectomy may be advisable to remove areas where desquamated material may build up and acquire salt deposits. Any measure to promote easy passage of wads is recommended. Multiple manipulations are necessary. If all desquamated material can be removed, attempt at eradication of infection is laudable but not usually successful. While keratin is present, control is considered satisfactory.

Reversal of the process, unless too well established with granulation, scarring, stasis, etc., may occur and should be strived for. Vitamin A does not accomplish this except in deficiency states. Irrigations are applicable to the bladder but wanting in respect to the renal pelvis though Stockman[20] reported apparent cure following 26 renal instillations of 1 per cent silver nitrate. We have not used papain but varidase and tryptar and solution G have been of no value. Ewert[21] reported apparent vesical cure using instillations of cod liver oil; in case 2 with reflux, our result was indeterminate. Helfert and Bremen[22] have successfully controlled a patient with bilateral renal leukoplakia using ACTH and systemic cortisone;

[18] Patch, F. S.: The association between leukoplakia and squamous cell carcinoma in the upper urinary tract. N. Eng. J. Med., **200:** 423–437, 1929.

[19] Utz, D. C. and McDonald, J. R.: Squamous cell carcinoma of the kidney. J. Urol., **78:** 540–552, 1957.

[20] Stockman, F.: Ein Fall von Epidermoidaler Metaplasie der Harnwege. Centralbl. Krank. d Harn u Sex. Org., **13:** 621–626, 1902.

[21] Ewert, E. E.: Use of cod liver oil in the urinary bladder for leukoplakia. Lahey Clinic Bull., **4:** 27–31, 1944.

[22] Helfert, I. and Bremen, H. A.: Leukoplakia of the urinary tract treated by ACTH. Ohio State Med. J., **49:** 109–110, 1953.

Shabad says these steroids normalize the urine but don't change the vesical lesion. In case 2 ACTH made the urine more clear only. Case 8 is taking cortisone at present. To my knowledge, cortisone has not been used topically. Capricol was used in case 8 for the desquamating effect of resorcinol but the trial was too short to evaluate. One wonders about the effect of podophyllin which affects mitosis in the meta phase and disrupts the stratum germinativum. One needs a few tolerant patients of leisure with vesical leukoplakia beyond control by fulguration on whom to try various forms of therapy which may be evaluated by periodic cystoscopic observation and biopsy.

CASE REPORTS

Statistical data are presented in table 1. However, each patient warrants some additional comments not suitable to tabulation.

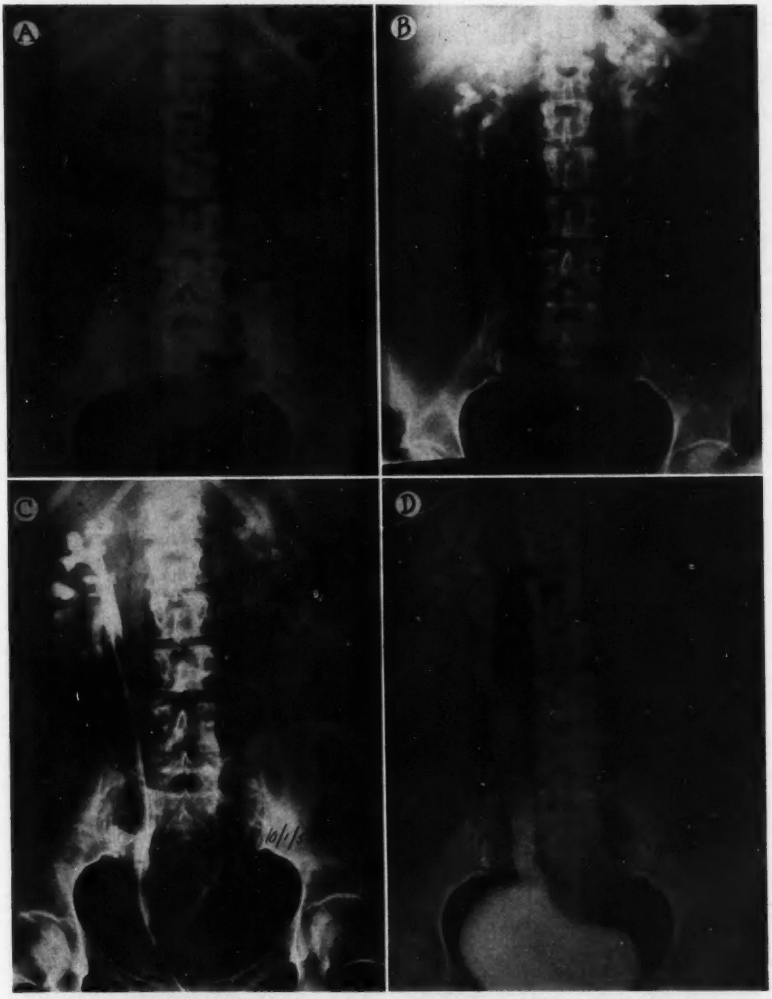


FIG. 2. Case 2. *A*, plain film 1958 unchanged from 1943 except faint density in left upper pole developed between 1956 and 1958. *B*, excretory urogram 1956, essentially same as 1946. *C*, October 1958, filling defect of keratin, lumbar ureter, remaining after manipulation of lower ureteral wads. *D*, cystogram shows present status after right partial nephrectomy, left nephrectomy, and open ureteral meatotomy.

Case 1. Fifteen cystoscopies had been performed before we saw this patient. We added 19 procedures to this including ureterolithotomy (1946) and right partial nephrectomy (1951). The left side was only occasionally symptomatic. Squamous carcinoma of the bladder was treated transurethrally in April 1956 (fig. 1, *A*) and also a recurrence in December 1957. Recurrence in January 1959 demanded cystectomy and 4 nodes were positive. He died of carcinoma in August 1959 but until July had felt the best in years. Procrastination in doing cystectomy because of the poor upper tract was wrong. The patient appeared to be pentothal sensitive.

Case 2. In 1943, a routine x-ray taken while the patient was pregnant showed an incidental right branch calculus and multiple left calculi. "Purulent material" was seen in the bladder at cystoscopy in 1948 because of a history of hematuria. In 1958 the patient noted sheets of membrane in the urine and shortly had repeated attacks of colic on both sides (fig. 2). In January 1959 a right partial nephrectomy was done and in July 1959 left pyonephrosis required nephrectomy. Attacks of

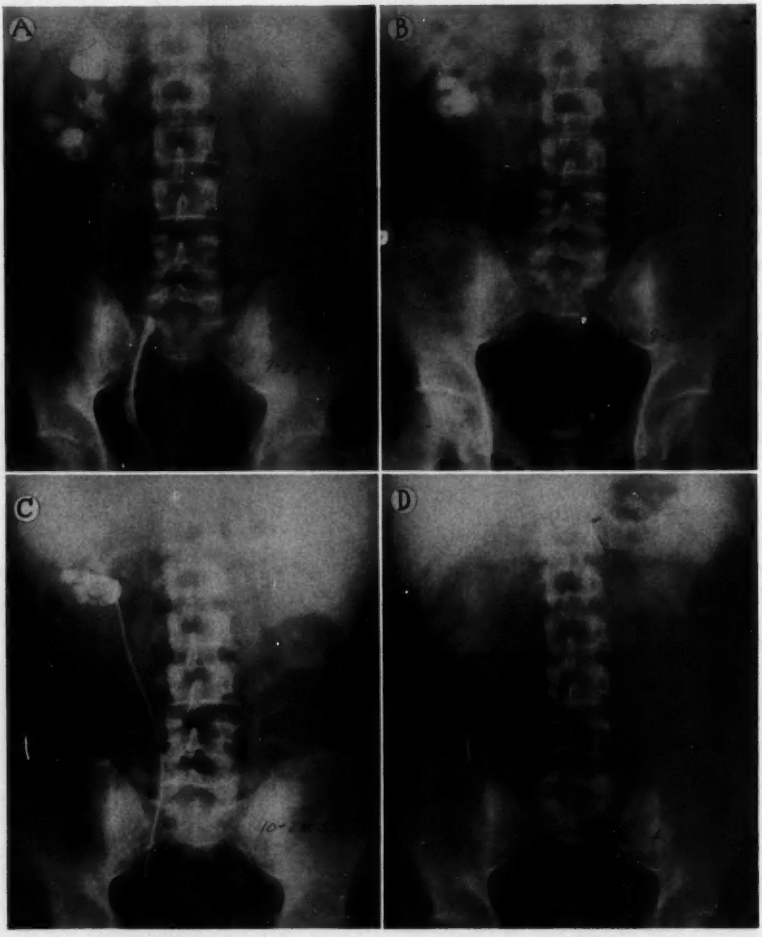


FIG. 3. Case 6. *A*, concentric layering of keratin may be seen in defect in pelvis; middle segment doesn't fill. *B*, excretory urogram after evacuation of much desquamated material. *C*, picture of cholesteatoma; it resembles infiltrative carcinoma. *D*, mottled calcification of salts deposited in layers of keratin.

right colic continued and a previous ureteral meatotomy was enlarged suprapubically to finger size in September 1959. Since then the patient has had no more colic but has had one bout of pyelonephritis. She recently passed a chunk with temporary urethral obstruction the only symptom. Is the reflux beneficial or detrimental? When she double voids, one visualizes an effect of turbulence in the kidney pelvis. Why did massive troubles suddenly appear after 15 years of known stone?

Case 3. This man had extensive metaplasia in his bladder (fig. 1, *B*) and was thought to have vesical and left renal tuberculosis in 1932 except that urine specimens were negative. Pain on the left side was relieved by ureterolithotomy in 1949; keratin was imbedded in the stone. Three years ago he passed two soft stones but has been asymptomatic except for mild frequency.

Case 4. When first seen this woman had carcinoma of the bladder associated with leukoplakia (fig. 1, *C*). Cystectomy and ureterosigmoidostomy were done in 1950. Left partial nephrectomy was done in 1952. Diversion was converted to an ileac loop in 1957. Right partial nephrectomy was done in 1958. She has continued to have occasional bilateral episodes of colic and infection but function remains fair.

Case 5. Episodes of right abdominal pain had occurred for 20 years but renal origin was problematical; several cystoscopies had been done. Although bilateral upper tract involvement has been known since 1953, the left side has remained asymptomatic and the right continued as before. In 1959 bilateral pelviolithotomy was performed and a constricted area of the right ureter (probably associated with stone impaction) was freed. Since then her only symptoms have been mild vesical irritation though bilateral reflux has been demonstrated.

Case 6. This father of 8 children had almost continual morbidity with no free interval of 6 months during our observation. Bilateral partial nephrectomies and multiple manipulations were done. He died in uremia with almost total renal destruction in 1958 (fig. 3).

Case 7. In 1938, the patient was in a sanatorium where a diagnosis of bilateral renal and vesical tuberculosis could not be verified. When seen in 1956 his blood pressure was 240/140. Bilateral pelvio-ileostomy (one loop) was done, followed later by cystectomy and partial prostatectomy. The vesical leukoplakia was unchanged by diversion. The ureters were almost entirely devoid of mucosa; it is astonishing that the kidneys survived with granulation-lined tubes for ureters. Right partial nephrectomy and pelvio-nephrolithotomy were done in 1958. His blood pressure is now 160/90 and he is in chemical balance (fig. 4, *A*).

FIG. 4. *A*, case 7. Present status; diversion has done well in preserving function
B, case 8. One dislikes thought of removal of kidney though process is active. Middle calyx has filling defect. Skeletal ankyloses also presents problem.

Case 8. I. F. received ACTH for 6–8 weeks in 1951. Symptoms of right colic appeared in 1956. Following nephrolithotomy and partial nephrectomy in 1960 a temporary renal fistula resulted from ureteral obstruction by epithelial masses. He recently had a series of attacks of colic and though left renal irrigations are negative for squamous cells, he is willing to continue with conservative measures. He is now taking cortisone (fig. 4, *B*).

Case 9. This young woman's visible mucosa looked normal when a renal leukoplakic mass was removed by pelviotomy after varidase irrigations had failed. She has remained well 2½ years; urine specimens are negative and films a year ago appeared normal. Although no squamous cells are present in the urine, perhaps another 10 years will be necessary to consider using the term cure.

DISCUSSION

Four cases in the literature have been followed from 1 to 30 months prior to nephrectomy done because of progression of symptoms. Five patients have had intentional conservative treatment. Stockman's patient has been mentioned. Keesal and Rosner[23] removed the epithelial mass from the renal pelvis and made a pelvioureteroplasty; filling defects were present in a pyelogram 3 months and 6 months later; there was evidence of hydroureter to the bladder. Eleven years later the patient was well. Urine specimens and urograms were negative.[24] Senger and Bottone[25] reported a patient with bilateral renal leukoplakia with continuing symptoms and unchanged pyelogram at 6 months. The patient of Naumann and Sabatini underwent nephrectomy for cholesteatoma; the remaining side had squamous cells in pelvic washings but the patient has remained asymptomatic for 7 years.[26] Helfert and Bremen's patient is of particular interest. He had bilateral disease treated with ACTH and cortisone; several attacks occurred to 1955. He noted the appearance of tissue in the urine several days before colic developed and at Dr. Helfert's suggestion began to take cortisone when the prodrome was noted. This stopped any further attacks. His excretory urogram in 1960 is unchanged from that in 1951 and he has had no disability for 5 years.[27] The patient of Abeshouse and Tankin[28] refused nephrectomy after left partial nephrectomy showed leukoplakia; he has signs of right renal and vesical leukoplakia but for 8 years has remained quite well except for pyuria and passage of tissue from the left.[29]

It appears that renal leukoplakia may be tolerated, in some instances, with relatively little morbidity for a long time. When keratin formation is rapid, distention associated with colic may cause peeling of the mucosa. If this accumulated mass can be passed, a free interval of weeks, months, or years may follow; if it does not pass, cholesteatoma begins. If attacks of colic (obstructed infection) are frequent, free drainage of the renal collecting system is mandatory if the kidney is to be preserved. Replacement of the ureter by ilium, as advised by Goodwin and Cockett,[30] for stone seems the most applicable method. This should have been done in case 6. Partial nephrectomy is often advisable. Stasis is eventual failure.

SUMMARY

Leukoplakia is probably reversible early in its course. The means of accomplishing this are not understood.

There is much variation in the clinical activity of the disease.

Once well established, the disease is progressive and, after much morbidity, fatal as regards the kidney and if bilateral, the patient.

Conservation entails a calculated risk but is mandatory in bilateral disease; since six of our 9 patients had bilateral involvement, the authors tend to favor conservatism.

The prevention of obstructed infection is the greatest single aim in the preservation of renal function when the process is well established.

ADDENDUM

Case 2 has again begun to accumulate material in the lowermost remaining calyx and its incorporation into the renal pelvis has been advised.

Case 8 decided upon right nephrectomy for physical, mental, and financial reasons. This was done June 12, 1961. Pathologic examination

[23] Keesal, S. and Rosner, A.: Leukoplakia of the renal pelvis. Urol. & Cutan. Rev., **51:** 717–720, 1950.

[24] Keesal, S.: Personal communication.

[25] Senger, F. L., Bottone, J. J. and Kelleber, J. J.: Bilateral leukoplakia of the renal pelvis. J. Urol., **65:** 528–531, 1951.

[26] Sabatini, S. A.: Personal communication.

[27] Helfert, I.: Personal communication.

[28] Abeshouse, B. S. and Tankin, L. H.: Leukoplakia of the renal pelvis and the bladder. J. Urol., **76:** 330–337, 1956.

[29] Tankin, L. H.: Personal communication.

[30] Goodwin, W. E. and Cockett, A. T. K.: Treatment of multiple, branched renal calculi by pyelo-nephro-ileo-vesical anastomosis. J. Urol., **85:** 214–222, 1961.

revealed leukoplakia and chronic pyelonephritis. He is asymptomatic and the urine is negative.

305 Medical Arts Bldg., Minneapolis 2, Minn.

ADDITIONAL REFERENCES

FALK, C. C.: Leukoplakia of the renal pelvis and ureter. J. Urol., **72:** 310–315, 1954.

KRETSCHMER, H. L.: Leucoplakia of the urinary organs. Surg., Gynec. & Obst., **47:** 145–154, 1928.

MCCREA, L. E.: Leukoplakia of the renal pelvis. J. Urol., **64:** 209–213, 1950.

LANDES, R. R. AND HAMLIN, J. T.: Leukoplakia of the renal pelvis. J.A.M.A., **155:** 1053–1054, 1954.

LOW, H. T. AND COAKLEY, H. E.: Leukoplakia of the renal pelvis. J. Urol., **60:** 712–713, 1948.

POLITANO, V. A.: Leukoplakia of the renal pelvis and ureter. J. Urol., **75:** 633–643, 1956.

SCOTT, F. B. AND THOMAS, A. M.: Clinical management of leukoplakia of the renal pelvis. J.A.M.A., **174:** 363–366, 1960.

THOMPSON, R. F.: Leukoplakia of the renal pelvis. Tr. South Cent. Sect., A.U.A., 1954, pp. 64–69.

Papers Relating to Metaplasia

FAGERSTROM, D. P.: Proliferative tumors of the ureter and renal pelvis, with further observations on the significance of "epithelial cell nests": Six case reports. J. Urol., **59:** 333–357, 1948.

MACLEAN, J. T. AND FOWLER, V. B.: Pathology of tumors of the renal pelvis and ureter. J. Urol., **75:** 384–415, 1956.

MOSTOFI, F. K.: Potentialities of bladder epithelium. J. Urol., **71:** 705–714, 1954.

PACK, G. T. AND BUZZANCA, R.: Experimental production of epithelial hyperplasia of the renal pelvis. Am. J. Surg., **7:** 221–228, 1929.

ROSS, C. A. AND KRAUS, G. E.: Effect of tobacco tars on regenerating tracheal mucosa. AMA Arch. Surg., **82:** 314–317, 1961.

SCHOLL, A. J.: Squamous cell changes and infection in the urinary tract. J. Urol., **44:** 759–767, 1940.

STIRLING, C. AND ASH, J. E.: Chronic proliferative lesions of the urinary tract. J. Urol., **45:** 343–360, 1941.

YOUNGBLOOD, V. H. AND KICKLIGHTER, J. E.: Squamous cell carcinoma of the renal pelvis. J. Urol., **67:** 54–59, 1952.

TECHNICAL ADVANCES IN THE PREVENTION OF URINARY TRACT INFECTION

ROBERT E. DESAUTELS, CARL W. WALTER, ROGER C. GRAVES AND J. HARTWELL HARRISON

From the Peter Bent Brigham Hospital, the New England Deaconess Hospital, and the Department of Surgery, Harvard Medical School, Boston, Mass.

It has been demonstrated previously that aseptic management of the catheter and the urinary catheter drainage system achieves a significant reduction in the usually expected incidence of urinary infection. The present paper describes further experience with this study and offers some simplifications and improvements for the management of catheter drainage.

METHODS

It is necessary to re-emphasize that asepsis is mandatory, regardless of the equipment used. Introduction of bacteria at the time of catheterization or cystoscopy is avoidable if proper technique is employed (fig. 1).

The area of the urethral meatus is washed with a surgical detergent containing hexachlorophene and then with 1:1000 or 1:750 benzalkonium chloride.* The distal urethra is irrigated with aqueous benzalkonium chloride, 1:1000, using an Asepto syringe, before the catheter or instrument, well lubricated with a sterile water-soluble jelly, is passed.

Daily cleansing about the urethral meatus with aqueous benzalkonium chloride (once a day in males, twice a day in female patients) followed by the application of a wet benzalkonium chloride dressing about the glans penis and adjacent catheter in male patients, or a catheter impregnated with tetramethylthiuramdisulphide, was used as a means of preventing the entry of bacteria around the catheter either at the urethral meatus or the cystostomy sinus or the nephrostomy sinus.

Once attached to the drainage set, the catheter is not detached unless absolutely required, and then only with careful disinfection of the junction by an excess of 70 per cent ethyl alcohol. No irrigations are carried out routinely, even in the postoperative cases and in the latter they are done only where specifically necessary. Two different sterile drainage sets were tested: one, a standard rubber tubing with glass connector proximal and adapter attached to a two-hole rubber stopper distally for use in a sterile one-liter bottle; the other, a sterile plastic tubing with a plastic drip chamber at its distal end as an air break to be used with sterile plastic bags and supporting frame* (fig. 2).

Urine was taken for culture and colony count at the start when indicated during drainage, and at end of period. Most cultures were either sterile or definitely positive, i.e. over 100,000 organisms per milliliter. A few had Staphylococcus albus or aureus in counts less than 1000 per milliliter and were considered of no clinical significance. Subsequent cultures proved this assumption correct.

RESULTS

Benzalkonium dressing. In 82 patients, benzalkonium cleansing about the catheter and a benzalkonium dressing were used (table 1). Forty-four patients had a suprapubic tube, and three of these had a positive terminal culture. Thirty-eight patients had a urethral catheter, and 11 of these had a positive terminal culture. In 18 of these patients, no antibiotic or sulfonamide was given, and a positive culture was obtained in two. Three patients with initial positive cultures had a sterile culture at the time the catheter was removed, following treatment with an antibiotic.

Impregnated catheter. In 73 patients, a catheter impregnated with tetramethylthiuramdisulphide was used, and nine of these had positive cultures when the catheter was removed (table 2). Fifty-five patients of this group had urethral catheter drainage; nine had positive terminal cultures. Of 13 on suprapubic drainage, one had a positive culture, and of five on nephrostomy drainage,

* Zephiran chloride; Winthrop-Stearns, Inc.

* Fenwal Bedside Drainage Set Y1980, Fenwal Labs, Inc.; Bardic Bags and Frame, C. R. Bard, Inc.

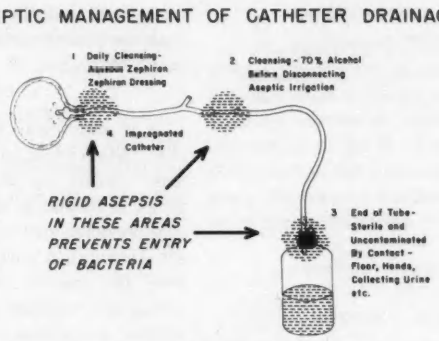

ASEPTIC MANAGEMENT OF CATHETER DRAINAGE
1 Daily Cleansing - Aqueous Zephiran Zephiran Dressing
2 Cleansing - 70% Alcohol Before Disconnecting Aseptic Irrigation
4 Impregnated Catheter
RIGID ASEPSIS IN THESE AREAS PREVENTS ENTRY OF BACTERIA
3 End of Tube - Sterile and Uncontaminated By Contact - Floor, Hands, Collecting Urine etc.

FIG. 1

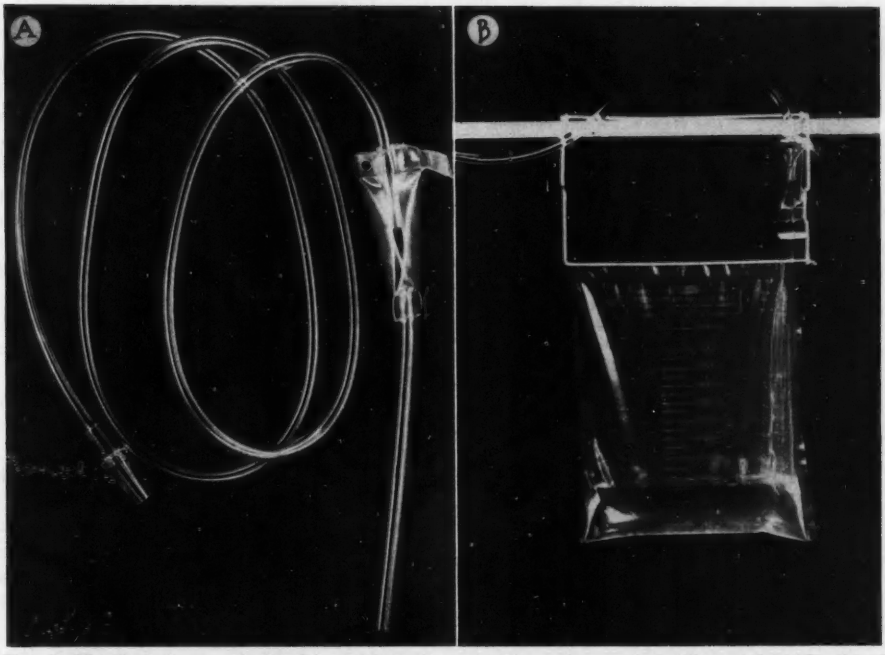


FIG. 2. Plastic drainage set with drip chamber. Large outflow tube prevents filling of chamber, thereby providing constant air break.

none had a positive culture when the catheter was removed. In this group, no medication was given in 30, and positive cultures were obtained in six of these 30 while on drainage. Two of the six were sterilized before the catheter was removed. Of 11 patients with initially positive cultures, eight had a sterile culture, after treatment with an antibiotic, at the time the catheter was removed.

Bottle drainage system. The bottle system was employed in 115 patients, and of these, 18 had positive terminal cultures (table 3). Eight of these positive cultures were believed definitely related to contamination of the end of the drainage system. Four of the 18 appeared related to inadequate care of the dressing, and three of the 18 appeared related to contamination at the connection of catheter and drainage set.

TABLE 1. *Catheter with benzalkonium dressing*

Terminal Cultures	Urethral	Suprapubic
Negative	31	41
Positive	11	3
Total	38	44

TABLE 2. *Impregnated catheter*

Terminal Culture	Urethral	Suprapubic	Nephrostomy
Negative	46	12	5
Positive	9	1	0
Total	55	13	5

TABLE 3. *Positive terminal urine cultures*

Apparent Cause	No.	Type of Apparatus
Contamination at surgery (long transurethral resection)	1	Impregnated catheter with plastic drainage set
Infected at start and throughout	3	Impregnated catheter with plastic drainage set
Contamination at urethral meatus (inadequate care of dressing)	3	Regular catheter with bottle system
Contamination at cystostomy sinus (inadequate care of dressing)	1	Impregnated catheter with bottle system
Contamination at connecting tube (tube disconnected without aseptic precautions)	3	Regular catheter with bottle system
	2	Impregnated catheter with bottle system
Contamination at end of drainage set (bottle overflowed, etc.)	8	Regular catheter with bottle system
Unknown	3	Regular catheter with bottle system
Total	24	

Plastic set with drip chamber. The new plastic drainage set with a drip chamber was used in 40 patients, and of these, six had a positive terminal culture (table 3). Two were related to contamination at the junction of catheter and connecting tube, one to probable initial contamination at time of surgery, and the other three were infected initially, keeping the same organism throughout.

The duration of drainage was at least 7 days in the average case with a variation of from 2 days to 6 months. Positive cultures occurred with no definite relation to the length of time involved.

DISCUSSION

It is significant that in cases under careful observation while on catheter drainage, a positive urine culture can almost always be related to a break in technique or a defect in the system. In most systems now in use, the end of the drainage set is a common port of entry for bacteria. Therefore, the use of an apparatus that prevents retrograde contamination is essential. Where routine irrigations of the catheter are carried out, contamination almost always occurs. Only with thorough disinfection of the junction of catheter and connecting tube and use of extreme care, can irrigations be done safely. This is usually lacking in the average hospital situation. Furthermore, irrigation is not needed when the urine is clear and sterile but only when a large amount of clot or debris is present. The use of bacteriostatic compound, either about the catheter or in the catheter substance, has resulted in a significant reduction in the incidence of positive cultures. The use of an impregnated catheter is simpler and probably more foolproof than the dressing. However, in the case of the short female urethra and short cystostomy sinus, it is still important to maintain good hygiene about the tube, because a sudden motion can conceivably carry an innoculum of bacteria-laden material from the external environment all the way into the bladder without inactivation by the catheter surface. Irrigating the distal urethra with aqueous benzalkonium chloride, which we have found to be perfectly safe, has eliminated the few bacteria (with a resulting low colony count) that were so commonly found in cultures taken at catheterization and cystoscopy before this maneuver was carried out. This is felt to be especially important in catheterizing female patients, because it is difficult to cleanse the meatus adequately by simple external washing. The use of a bacteriostatic lubricant may also be of value.

Prophylactic anti-bacterial treatment is not essential. However, where a single contaminating episode has taken place it is of value. When a steady stream of bacteria is entering the urinary tract, prophylactic treatment selectively preserves the resistant competitors. As indicated by the aforementioned statistics, an attempt to

sterilize an infected urinary tract is definitely worthwhile in the patient on catheter drainage, provided that new bacteria are prevented from entering the system.

To date, the simplest and most effective system for catheter drainage appears to be the catheter impregnated with tetramethylthiuramdisulphide and the plastic drainage set with drip chamber for use with a plastic bag.

SUMMARY AND CONCLUSIONS

It is emphasized that aseptic technique is essential in the use of the catheter and catheter drainage system. Maintenance of a closed system with a bacteriostatic catheter to prevent entry of bacteria about the meatus, and an air break at the end of the drainage tube to prevent retrograde invasion of bacteria, protects the urinary tract from infection.

CHANGES IN BACTERIAL ENZYME PATTERNS, DRUG SUSCEPTIBILITY AND CHEMOTHERAPY THROUGH ENZYME BLOCKING AGENTS

H. SENECA, J. K. LATTIMER, H. H. ZINSSER, J. T. DONOVAN, P. PEER AND P. H. STUART

From the Department of Urology, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York, N. Y.

The successful use of urease blocking agents, such as chlormerodrin, to acidify the urine in cases with intractable urea splitting infections was reported previously from our laboratory.[1] Magnesium ammonium phosphate stones (struvite) in the urinary tract are usually associated with urea splitting pathogens which raise the pH of the urine. Urease blocking agents lower the urinary pH, rendering it acid, and thus may prevent the recurrence of such stones.

It was found that in vivo and in vitro exposure of bacteria to urease blocking chemicals induced morphological and physiological changes in some organisms.[2] These changes were usually favorable to the host in that the pathogen became more drug susceptible. On the other hand, if susceptible organisms were so treated, drug resistance was sometimes made worse. These changes included alteration in the morphology, staining features, fermentation reactions, and drug susceptibility.

One of the simpler methods of studying the changes occurring in DNA is by observing the activities of cellular enzymes. On the basis of the urease and citrase production, the pathogenic bacteria were classified into seven categories or profiles.[2] The effects on other enzyme systems have also been studied.[3] Urea-splitting pathogens are those which produce ammonia from urea in live cultures. This reaction can be easily observed in cultures when urea is added, and an indicator (phenol red) which becomes red when the pH is raised because of ammonia production. The urea-splitting bacteria might better be referred to as urea-secreting or producing because the activities of this enzyme can be observed in live cultures.[4] P. columbiensis, P. morganii, Klebsiella, Aerobacter, Staphylococcus (70 per cent) and Pseudomonas (77 per cent) are the only known urea splitters. When urea is not split by live cultures, the organism is referred to as non-urea splitting or non-urease secreting or producing. All the other pathogens are in this class. It is known that urease does not diffuse or permeate through the cell wall and is not found free in the surrounding milieu. Studies are in progress to determine the mechanism of urea splitting through the utilization of N^{14} urea.

It was observed that the urease secreting bacteria were either drug resistant or readily became drug resistant when they were exposed to antibacterial chemotherapy. On the other hand, non-urease secreting bacteria were drug sensitive and mutation was infrequently observed.[1, 2]

What is bacterial urease? It is a macroglobulin having a molecular weight of 473,000 containing 31 sulfhydryl groups with an isoelectric point of 5.0, optimum pH of 7.2 to 7.5, dialyzable, absorbed on Seitz filter, but filtrable through millipore HA, does not permeate through the cell wall, active at 70° C, catalyzes the hydrolysis of urea to carbon dioxide and ammonia through the mechanism of sulfhydryl groups, thus mercaptide forming reagents such as cysteine causes its reversible inactivation, by oxidation beyond —S—S— stage. It is blocked by heavy metals (mercury, silver and copper), occurs in a variety of bacteria, yeasts, molds, plants, molluscs, gastric mucosa, liver, kidney and erythrocytes.[5, 6] Among 5 Pseudomonas strains which were non-urea splitting, two of the survivors of sonic oscillation became urea splitting in live cultures in

[1] Zinsser, H. H., Lattimer, J. K. and Seneca, H.: Aerogenosis: A plea for clinical bacteriology. J. Urol., **83:** 755, 1960.

[2] Seneca, H., Lattimer, J. K. and Zinsser, H. H.: The chemotherapy of urease and citrase producing bacteria of the urinary tract. Ann. Int. Med., **53:** 468, 1960.

[3] Seneca, H. and associates: Enzyme profile of bacteria based on Krebs' cycle substrates. Unpublished data.

[4] Seneca, H., Lattimer, J. K., Stuart, P. H. and Peer, P.: Urease activity of sonic lysates of pathogenic bacteria. Lancet, **1:** 1166, 1961.

[5] Walberg, C. B.: The Purification and Properties of Bacterial Urease. University of Southern California School of Medicine, 1957.

[6] Seneca, H., Stuart, P. H., Peer, P. and Nally R.: Unpublished data.

subsequent generations. Of 7 Staphylococcus strains which were non-urea splitting, two of the survivors of sonic oscillation also became urea splitting in subsequent generations. It is early to speculate the genetic significance of this finding yet these changes are definitely related to the physiochemical alterations in the cell wall. If we reason that DNA of the nucleus is the ultimate focus of changes that take place in a cell, then, such a change is inherent in DNA. However, we cannot overlook the possibility that the cell wall may also play a role in genetics or inheritance.[6]

Previously the in vitro and in vivo as well as the clinical results with chlormerodrin were reported.[1, 2] Lately our studies revealed that RO 5-2795 or N-(3-chloromercury 2 methoxypropyl) 5-methyl 3 isoxazole carbamide and 5-3211 or N-(3-chloromercury 2 ethoxypropyl) 5-methyl 3 isoxazole carbamide are effective urease inhibitors, but have the additional advantage over chlormerodrin in having potent antibacterial effect against Staphylococcus, Streptococcus and enterococcus. For live cultures, urease of 6 urea splitting bacteria (P. columbiensis, P. morganii, Aerobacter, Klebsiella, Pseudomonas and Staphylococcus) was blocked by RO 5-2795 in 0.01 to 1.56 μg. per ml. while chlormerodrin blocked it in 0.19 to 3.12 μg/ml. When urease was obtained by sonic lysis from both urea and non-urea splitting bacteria (Proteus, Klebsiella, Aerobacter, Escherichia, Salmonella, pneumococcus, enterococcus, Streptococcus and Staphylococcus), urease was blocked by chlormerodrin and RO 5-2795 in 0.19 to 12.5 μg./ml. Among 64 strains of resistant Staphylococcus, 64 were resistant to chlormerodrin, but only 11 were resistant to RO 5 2795, and 53 were quite susceptible. In vitro mutation studies indicated that urea splitting bacteria developed greater degree of resistance or tolerance to chlormerodrin than to RO 5-2795. Moreover, in vitro studies indicate that there is synergistic effect when an organic mercurial such as RO 5-2795 and an antibiotic/antibacterial are combined. Most marked synergism is observed when the mercurial is combined with sulfonamide, colymycin, chloramphenicol, streptomycin and nitrofurantoin.[7]

[7] Seneca, H., Lattimer, J. K., Stuart, P. H., Peer, P. and Nally, R.: In vitro studies on a new urease blocking agent. In press: Antibiotics and Chemotherapy.

TABLE 1. *Chronic urinary tract infections treated with enzyme blocking drug alone (RO 5-2795). Fifty-five of 126 cases on the drug documented*

Organism	Total	Cured	Failed	Reinfected
E. coli	11	1	10	
A. aerogenes	11	2	9	1 with B. proteus
K. pneumoniae	5		5	
B. proteus	7	1	6	1 with A. aerogenes
P. aeruginosa	3		3	
E. intermedia	1		1	
Paracolon	2	1	1	
S. marcescens	1		1	
Enterococcus	10	7	3	
Staphylococcus	3	2	1	1 with E. coli
Streptococcus	1	1		
	55	15	40	3

RO 5-2795 is a white crystalline powder which is administered in tablet form, weighing 21.5 mg. per tablet representing 10 mg. nonionic mercury. Studies in dogs and rats indicate that it does not possess unusual toxic potentials. Rats tolerate 25 mg./kg. for 6 weeks without the occurrence of toxic symptoms, changes in the hematological picture and nutritional condition of the animals. Similarly, dogs tolerate 25 mg./kg. very well. No changes in the liver and kidney functions were observed, and no alteration of the fluid electrolyte balance was reported.[8]

CLINICAL OBSERVATIONS

As of the writing of the manuscript, 126 ward and out-patients were treated with enzyme blocking drug, RO 5-2795. Almost all of these patients were suffering with chronic resistant urinary tract infections, ranging from pyelonephritis at the upper end of the excretory system, to urethritis at the terminal end.

As soon as the patient was admitted to the ward, or seen by the physician in the out-patient clinic, a urine specimen was obtained under sterile conditions for cultural purposes. In the female, it was obtained by catheterization; and in the male, mid-stream specimen. The patient is then given one tablet of RO 5-2795 4 times daily, after meals, for 4 days. During this period, the urine is cultured on blood brain heart agar, EMB agar and brain heart broth. In case there

[8] Hines, L.: Personal communication, Hoffmann LaRoche Laboratories.

is no growth, the incubated urine is replated. The organisms are identified, the enzyme profile determined on the basis of urease and citrase, as well as the fermentation of carbohydrates.

During the 4 day period when the patient is on enzyme blocking therapy, the drug sensitivity pattern of the pathogen is determined using the tube dilution method. If at the end of enzyme blocking therapy, the urine culture is still positive, then the drug of choice is given for another five to seven days, and a third culture is obtained.

Routine blood counts, urinalysis, blood electrolyte levels and, when necessary, bromsulphalein and phenolsulfonphthalein estimations were performed. It was the policy not to administer this mercurial to any patient who had an elevated blood urea nitrogen, renal dysfunction or who was in coma.

Fifty-five cases have been documented carefully, the rest are either incomplete, or had negative urine cultures. Table 1 shows the effect of RO 5-2795 in 55 patients who were given a total of 16 tablets in 4 days. Fifteen organisms disappeared. Three patients became reinfected with another organism and 40 were failures. The successes included 7 enterococci, 2 Aerobacter, 2 Staphylococcus; one each of Escherichia, Proteus, Paracolon and Streptococcus were cured. One Aerobacter was reinfected with B. proteus, one B. proteus reinfected with Aerobacter and one Staphylococcus reinfected with Escherichia.

Twelve of the 40 failures were subsequently given the drug of choice with 5 cures and 3 reinfections. One Pseudomonas was reinfected with enterococcus and Staphylococcus, one enterococcus re-infected with Escherichia and one Staphylococcus reinfected with B. proteus. The cures were one of Escherichia, Proteus, Pseudomonas, enterococcus and Staphylococcus (table 2).

Thus, enzyme blocking drug alone removed bacteria from the urine of 15 patients, whereas

TABLE 2. *Twelve of 40 failures on enzyme blocking drug subsequently were treated with antibacterials or antibiotics*

Organism	Total	Cured	Failed	Reinfected
E. coli	3	1	2	
A. aerogenes	1		1	
K. pneumoniae	2		2	
B. proteus	2	1	1	
P. aeruginosa	1	1		1 with enterococcus + staphylococcus
E. intermedia	1		1	
Enterococcus	1	1		1 with E. coli
Staphylococcus	1	1		1 with B. proteus
	12	5	7	3

TABLE 3. *Drug sensitivity changes in bacteria after exposure to enzyme blocking drug (RO 5 2795) in patients*

Organism	Total	RO 5 2795		Sulfisoxazole		Tetracycline		Declomycin		Chloramphenicol		Kanamycin		Nitrofurantoin		Colymycin		Streptomycin	
		Sen	Res	Sen	Res	Sen	Res	Sen	Res	Sen	Res	Sen	Res	Sen	Res	Sen	Res	Sen	Res
E. coli	11	3	4	2		1	1	1		1		4	1	3	2	4		4	
A. aerogenes	11	2	2	3	1		2	1	2	2	3		3	3		2	3		
K. pneumoniae	5		2	2								1	2			2			
B. proteus	7	1	3	3	1		1	1	1	1	1		1					1	
P. aeruginosa	3				1	1			1										
E. intermedia	1		1		1					1			1						
Paracolon	2		1	1															
S. marcescens	1	1		1		1		1		1		1							
Enterococcus	10		1	1		1				1		1							
Staphylococcus	3												1						
	54	7	14	13	4	4	3	4	4	7	4	7	9	6	2	8	3	5	

SEN = became more sensitive. RES = became more resistant

it failed in 40 cases. When twelve of the latter were given the specific drug of choice, there were an additional 5 cures.

Table 3 shows the changes in the drug sensitivity pattern in pathogenic bacteria after in vivo (in patients) exposure to urease blocking drug RO 5-2795. Seven organisms became more sensitive and 14 more resistant to RO 5-2795. Thirteen became more sensitive and four more resistant to sulfonamide; seven became more sensitive and 4 more resistant to chloramphenicol; eight more sensitive and 3 more resistant to colymycin; six more sensitive and 2 more resistant to nitrofurantoin; seven more sensitive and 9 more resistant to kanamycin. With tetracycline and demethylchlortetracycline there were almost the same number which became more resistant or sensitive. Five became more sensitive to streptomycin and no increased resistance was observed.

Side effects. Four patients had diarrhea, three had dizziness, two had diarrhea and dizziness. One patient had to stop the drug temporarily because she felt nauseated but then resumed treatment.

It is apparent that this drug is a powerful weapon which produces profound changes in the metabolic functions of the bacterial cell, probably by acting on a variety of enzymes by way of the sulfhydryl groups.

Previously we speculated that urease blocking agents should be effective against urea splitting bacteria. It was rather surprising that a number of non-urea splitting bacteria were also killed both in vitro (RO 5-2795) and in vivo (chlormerodrin and RO 5-2795). Since then, we have reported the presence of urease in all the pathogenic bacteria (30 genera) we examined. The sonic lysates of all contained urease. Therefore, we can understand the possible use of an organic mercurial compound as a urease blocking agent in all bacterial urinary infections because of natural occurrence of urease among all pathogens tested. We may expect that urea is the most available nitrogen source to bacterial metabolism for incorporation into amino acids.

SUMMARY

Urea splitting and non-urea splitting bacteria had urease within their cell bodies. Non-urea splitting strains of Pseudomonas and Staphylococcus gave rise to urea splitting mutants following exposure to sonic oscillation.

Urea splitting bacteria were: P. columbiensis, P. morganii, Aerobacter-Klebsiella group, Pseudomonas (77 per cent) and Staphylococcus (70 per cent). The remaining pathogenic bacteria were non-urea splitting.

Bacterial urease was non-diffusible through the cell wall, dialyzable, absorbed on Seitz filter, filtrable through millipore HA, inactivated at 100° C, had a molecular weight of 473,000, contained 31 sulfhydryl groups, was a macroglobulin, could be blocked by heavy metals such as mercury, silver and copper.

Chlormerodrin, RO 5-2795, and RO 5-3211 were potent urease inhibitors; the latter two were also potent antibacterial agents against some gram-positive cocci even when used alone.

In vivo exposure to RO 5-2795 in patients induced physiological and morphological changes in pathogenic bacteria. These changes in the metabolic pattern in the previously drug resistant bacteria were usually but not invariably in the direction of increased drug susceptibility.

In vitro synergism was observed when an enzyme blocking drug was combined with an antibacterial or antibiotic.

One hundred twenty six patients with chronic urinary tract infections, caused by a variety of gram-negative rods and gram-positive cocci, were treated with RO 5-2795. Fifty-five cases were systematically documented: 15 were bacteriologically cured with enzyme blocking agents alone, with three re-infections. Twelve of 40 failures on enzyme blocking drug alone were subsequently treated with specific antibacterial drugs, with five cures and three re-infections; thus when enzyme blocking and enzyme blocking plus antibacterial drug therapy was used seriatum combined, the results indicated that there were 20 cures with 35 failures.

The reversal of drug resistance in many strains, by these enzyme blocking agents, was of interest.

DISCUSSION

DR. GRAYSON CARROLL (St. Louis, Mo.): Leukoplakia and renal papillary necrosis are very different, but their symptoms are similar. We have had 2 cases of leukoplakia that were not submitted to surgery. Also, we have had 2 patients with papillary necrosis.

I would like to present briefly one of these cases so as to bring out one or two facts which I think should be emphasized. The patient was a very active man, one of the executives of the Chevrolet plant in St. Louis. Acute colic developed on the left side.

Examination revealed no evidence of calculi, although he did have a Pseudomonas infection. His intravenous urograms, retrograde pyelograms, and his story that he passed shreds led me to make a tentative diagnosis of leukoplakia of the kidney. The boys on the service were almost scoffing at the idea because they said, "How can you flatly make a diagnosis of that kind?"

I don't believe it is as hard to make a diagnosis as has been thought, especially when a patient has colic and says that he is passing shreds or plugs. We told this man that if he passed a plug, to bring it to us; it wasn't very long before he did.

The laboratory report on the specimens stated: "The two specimens were received. One consists of small flakes of material. The other consists of numerous fragments of material which are necrotic in appearance, making a total mass of 10 mm. in diameter. Sections of bulk pieces show superficial stratified squamous epithelium with marked keratosis. The larger piece shows nothing but keratonized material, apparently from squamous epithelium. There are numerous colonies of bacteria in both pieces." I think that establishes definitely the diagnosis without question.

The Pseudomonas was resistant to everything by the sensitivity discs except colymycin. We prescribed 30 mg. every 6 hours around the clock for 5 days, at the conclusion of which the urine was clear and the cultures negative.

Later, the infection recurred. Interestingly enough, we found Pseudomonas in the prostatic secretion. That was obtained by having the patient void part of the urine and then massaging the prostate and letting the secretion drop into a culture tube. On three or four different instances we obtained pure Pseudomonas.

The patient was ambulatory and did not have any symptoms. We gave him 60 mg. colymycin at a single dose daily for 5 days. The Pseudomonas responded to the drug. We are now studying the possibility of giving single doses of colymycin, which, of course, would greatly increase its usefulness because it then can be used in the office.

Some workers have indicated that this drug is bactericidal to the Pseudomonas in 80 minutes; you can maintain a high blood level with colymycin of 60 mg. over about a six-hour period. It does seem reasonable that that can be done.

I would like to say that colymycin has now been passed by the Food and Drug Committee and is now available. We have prescribed the drug for about three hundred patients, and we have had no increase in side effects except that some notice a little tingling around the face. Nothing serious has been observed.

I would like to ask the essayist if he thinks that infection has something to do with the production of leukoplakia. Also, I notice that some of the cases that were presented persisted as long as ten years. How serious is the prognosis?

Our cases were bilateral, and I don't know any other treatment except antibiotic drugs.

DR. FRANK HINMAN, JR. (San Francisco, Cal.): I think Dr. Desautels and Dr. Harrison's paper needs discussion. There are two aspects to this problem of infection secondary to the catheter. One would be the medico-legal; the other would have to do with what we have chosen to call the bladder defense mechanism.

First the medico-legal: I think that we have all adopted too much of a laissez-faire attitude—and I don't think this is necessarily justified—to the free introduction of bacteria into the bladder. At our hospital patients are beginning to question whether they should pay their hospital bill if they pick up a drug-resistant infection with its complications

As far as the bladder defense mechanism is concerned, we became interested in this a year or two ago. Dr. Cox, one of our residents, has been working with me on this. What we did was to take eighty young normal patients who had indwelling catheters for varying periods of time from 24 to 72 hours. In contrast to what we read in the literature, at 24 hours only 6 per

cent of them had infection. This was not a hundred thousand colonies per cubic centimeter; this was less than a hundred colonies per cubic centimeter. This was with no precautions; this was with routine county hospital catheterization and routine care of the catheter with all the detachments and bags and floor bottles that go with it. Even at 72 hours, less than half—46 per cent. Dr. Cox is going to report this before the American Medical Association next fall.

This got us thinking about bladder defense mechanisms. We are going to talk more about this at the American Urological Association meeting. It would appear that what we are dealing with is not asepsis or contamination. Those are two separate phenomena. Rather we are talking about a problem of relative contamination. If we can keep the bacterial population in the urethra and in the catheter tube to a minimum, the normal bladder is able to take care of it and can eradicate the bacteria due to the activity of its own mucosa. However, if we unwarrantedly contaminate the catheter as we so often do after operation with our unsterile irrigation, leaving the end of the tube under contaminated urine and all the other breaks in technique that we use, then this bladder defense mechanism is unable to take care of the infection which is introduced. Then infection results.

Dr. J. Hartwell Harrison (Boston, Mass.): With reference to Dr. Baxter Smith's excellent presentation, I thought I might show here the ultimate in renal leukoplabia which has progressed to epidermoid carcinoma in a patient who had necrotizing pyelonephritis which was very diffusely spread throughout the kidney. Unfortunately, a thoracic surgeon had not paid enough attention to the findings in her urine 3 years before, for a left pneumonectomy was done because of epidermoid carcinoma which had metastasized to the left lung. Subsequently this lesion was discovered.

I would like to add that we have felt that Dr. Desautels' work—and this is his work, not mine—had been very important and exceedingly helpful to us. The Brigham and the New England Deaconess are the hospitals that have been following his very conscientious techniques. He is like a tenacious bull dog the way he goes after and maintains excellent catheter care in each of these institutions.

Dr. Baxter Smith: Dr. Carroll asked about the role of infection in producing leukoplakia. Almost all the patients whose cases have been reported have had infection; however, some have not when they were first seen. In view of the fact that the duration of the stasis and obstruction and so forth goes for many years sometimes before the patient is initially investigated or at least reported, one would expect that the infection would be very high at that period of time. Whether it is related to the process or not is problematical.

Dr. Carroll also asked how serious is the prognosis. One-sixth of the individuals reported have had carcinoma and squamous carcinoma of the kidney, which is not a very satisfactory disease. If one is going to treat the patient conservatively, he has to keep in mind that he is running some risk on that score and also hazarding the patient's life by being conservative if the lesion is unilateral.

The disease has episodes of obstructed infection. With each one, a group of nephrons is knocked out. Eventually the patient runs out of sufficient nephrons to get along. Survival of the kidney for a long period of time or for a short period of time depends on whether the squamous epithelium desquamates in small quantities and rather continually—in other words, sheds—or whether patients wad up this material in sufficient quantity, store it in the calyx or segment, then dump it out in the pelvis and add some more to it and get repeated episodes of obstruction.

I might cite Baselin's case again. The individual was 19 or 20 when he had symptoms over a period of two years. Following that he was symptom free for 10 years. Then he began this round of attacks of colic and he passed this kilogram of material.

Sometimes this formation is extremely rapid. One lady is reported to have had 3½ pounds of it in her bladder at death.

It also is fairly benign sometimes. But if it is well established, it is fairly lethal.

Dr. Desautels: Apparently this is a controversial subject in some respects, but it was started purely as an academic exercise. About four years ago the question came up: Why did 100 per cent of our patients—and it was just about 100 per cent—following prostatic surgery have a positive urine culture? Surprisingly, the answer was fairly easy and forthcoming once we started to be a little bit rigid about our technique and apply

these various principles to the various ports of entry.

I don't want to stir up a hornet's nest as far as medico-legal aspects of this business are concerned. I have thought about this myself as a potential problem. I suppose that it is more likely in California than in our part of the country.

The urinary tract certainly does have a resistance to bacterial invasion. There is no question about it. We see self-limited infections of the urinary tract all the time. In spite of the fact that before all of this, 100 per cent of our patients ended up with positive cultures, certainly within a month or two (often whether we treated them or not) their urine cultures were sterile.

However, in the immediate postoperative period, there is a definite morbidity that we all recognize in relation to the presence of bacteria in the urinary tract. The classic, common example of this is the occurrence of epididymitis. In this group of patients—it is not a large group, but these 155 patients—most of these individuals had prostatectomy and most of them were on drainage for sometimes as long as a month or six weeks. Yet only one of these individuals had epididymitis. He is the one whose rectum I entered while doing a perineal operation. There are definite benefits to be gained from this kind of fussy technique.

One final point isn't hard to carry out with the present setup of an impregnated catheter in the new drainage set. It is what I call a do-nothing system because it is less work for the nurses, less work for the doctors, and certainly it is cheaper as far as the use of antibacterial agents is concerned. Thank you.

Dr. Edgar Burns (New Orleans, La.): This first slide is that of a male who was first seen in our department at the age of seven months. The only thing that called attention to any abnomality in this child's external genitalia at birth was rather markedly redundant scrotum. It was on that basis that a more detailed examination of the genitalia was done at that time.

In addition to the redundancy of the scrotal tissue, this child was also found to have maldevelopment of the corpus spongiosum. [Slide] You can see here the marked redundancy in the scrotal tissue.

[Slide] With the scrotal tissue pulled back, you see it is a rather normal looking scrotum. You can see the urethra opened in the normal position in the glans penis, but there was a marked ventral curvature. It is the same type of development phenomenon that you see in hypospadias. You don't have an ectopic meatus.

[Slide] The skin biopsy in this case shows chromatin bodies in a great many cells. At that time we did not do any further studies. We sent these sections over to Dr. Bunge, and he agreed that these were atypical female type distributions of the chromatin.

At the age of 18 months, we felt that we should go further with the study in this child because of the failure to palpate any scrotal tissue—I mean any testicular tissue either in the scrotal or in the inguinal area—and in view of the presence of a positive chromatin pattern. We explored the child's abdomen. There were no internal female genitalia. There was a sort of rudimentary type of vas, which petered off into nothing. There was nothing in the inguinal areas. After that, we opened the scrotal sac on each side. No testicles were found in any place. There was nothing in the scrotum except a fatty type of tissue. A biopsy of this fatty type of tissue showed nothing but fat on histologic study.

This is a patient who has a normal type of penis except for the ventral curvature produced by a maldevelopment of the corpus spongiosum.

In addition to that, on this second admission, we cystoscoped the child with an infant type of instrument. He has a normal-looking male prostatic urethra. The verumontanum is about average for one in that age group. This is a male with positive chromatin pattern without any gonads of any type.

[Slide] This next case serves no purpose insofar as Dr. Bunge's presentation is concerned except to emphasize the importance of careful study in these children who show any abnormality in the genitalia.

We saw this child at the age of 7 weeks, at which time this picture was taken. You can see the marked enlargement of the clitoris.

[Slide] The vaginal orifice was perhaps a little smaller than average for an infant. At the same time, consulting with the Departments of Gynecology and Endocrinology, we felt that this child was female and should be raised as a female since the vaginal cavity was perfectly normal.

The 17-ketosteroids in this case were normal, but the buccal smears showed a male pattern. In view of the fact that this vaginal orifice and

the vaginal cavity were normal—the vaginogram showed a perfectly normal cavity for an infant—we felt that this child should be raised as a female but did nothing else at that time.

At the age of 2½ years, we saw the child again, repeated the studies, and the buccal studies showed the same—I'm sorry. Did I say chromatin positive or chromatin negative? Chromatin negative. We repeated the buccal smears and again got a chromatin negative pattern.

At that time we explored the abdomen. The child had a perfectly normal uterus and fallopian tubes. At the end of the right fallopian tube there was a perfectly normal-looking testicle. [Slide] There is the biopsy of the gonad before it was removed. There is a little tissue lateral to that which we biopsied looking for ovarian tissue. That is epididymis.

A careful search of the biopsied side showed no ovarian tissue in either a normal or abnormal position. We simply removed the testicle.

I want to repeat that the only purpose that this case serves in connection with Dr. Bunge's paper is to emphasize the importance of careful study in all of these children who have any abnormality of the genitalia that is recognized at birth.

Dr. John K. Ormond (Pontiac, Mich.): I had the pleasure of visiting Dr. Burns this spring. He had a patient he had sort of saved because of certain medico-legal implications. They figured that by the time this child had become an adult, I would have retired for the hills of Virginia so that it was better for me to do the operation.

This child at the age of two had shown marked macrogenitosomia praecox and later showed necrosis of puberty.

His physician in the bayou country—I say "his" in quotation marks—had prescribed cortisone, 25 μg. per day. He had done this without measuring ketosteroids. The drug was not effective because the child's pattern of growth was never normal.

[Slide] We see the child now at the age of ten, sort of an infant Hercules who has a palpable prostate by rectal examination. Above that, was a mass which we assumed later to be uterus because on panendoscopic examination a vagina opened into the urethra just at the verumontanum. These were beautifully outlined by urethrograms by Dr. Schlagel.

The ketosteroids of 90 had been suppressed over a period of 3 months of adequate therapy, Dr. Bunge. We explored this child, feeling that menstruation would probably begin soon. I failed to mention that this is an atypical chromatin positive "male." Obviously this was a female. At laparotomy we found a normal uterus with ovaries that looked essentially normal. Frozen section—and I don't have the permanent section reports—described these as probable ovotestes because structures reminiscent of seminiferous tubules were found as well as ovocytes.

[Slide] The next slide just shows the phallus, which is hypospadiac. There were no testes, of course, in the scrotum.

Question: The permanent sections did show testes?

Dr. Ormond: Permanent sections did show ovotestes.

I would like to ask Dr. Bunge this question with regard to Dr. Lawson Wilkins' work: If this child had been given adequate corticotherapy in infancy and carried along, would you anticipate that a normal growth pattern could have been accomplished? Thank you.

Dr. Bunge: Dr. Harrison's case here is rather complicated because it is apparent that the A. G. syndrome is present and also, ovotestes are present. It is quite likely that even by suppression with cortisone therapy that the interstitium of the ovotestes would produce sufficient androgen to virilize this child. I would like very much to take a look at those slides. Are they available?

Dr. Harrison: I'll send them to you.

Dr. Bunge: Fine. I would like to see those.

Dr. Burns's comments about the adequate investigation of these patients: I only wish to re-emphasize that it is only by careful study that one arrives at a solid diagnosis. I have at the present time 11 cases of male intersex with fallopian tubes, ureteri, vaginae, and all sorts of variations. In another year, I might get together those 11 cases.

About Dr. Burns's other case of chromatin positive without testes, I very facetiously one day in the laboratory said that we might well see the whole spectrum here of one testis absent; then, perhaps, a patient with no testes who would be chromatin positive, and he has filled that void. The other two possibilities, of course, are two testes without a patient and an egg with an XXY chromosomal constitution. [Laughter] [Applause]

INVESTIGATIONS ON UROLITHIASIS. II: STUDIES ON OXALATE

PAULO F. DE ALBUQUERQUE AND MILAN TUMA

It is well recognized that our present knowledge of oxalate metabolism is very limited. This probably accounts in part for the difficulty in controlling many cases of recurrent oxalate renal lithiasis.

The exogenous origin of oxalate seems to play a very minor role, if any, in stone formation. It has been repeatedly demonstrated that the insoluble salts (calcium oxalate) are not absorbed but are eliminated in the stools.[1] The soluble salts (sodium oxalate) are partially absorbed but even if all the many necessary requirements for its absorption are present, the increase in urinary oxalate excretion varies between 2.3 and 4.5 per cent of the total amount of sodium oxalate administered.[1]

It seems that most oxalate found in the urine is of endogenous origin. However, the exact starting point of it and the different steps in its metabolism are poorly understood; the scattered knowledge on the subject lends itself chiefly to speculation rather than to a real understanding of the metabolic process concerning oxalic acid and oxalates. There is general agreement that the organism is capable of synthetizing oxalate, as individuals in prolonged fast continue to excrete it in the urine.[2]

It has been demonstrated that a deficiency of magnesium can lead to an increase in the urinary excretion of oxalate, the process being reversed when magnesium is supplied.[3]

Three different hydrates of calcium oxalate are found: mono-, di- and trihydrate. The monohydrate is stable at temperatures above freezing, while the di- and trihydrates, according to some authors, are unstable and by losing water of crystalization are changed into the monohydrate, this process being influenced by several factors.[3, 4]

The calcium oxalate precipitated in the urine as oxaluria is the dihydrate.[3, 4] This form has also been found in the peripheral layers of oxalate stones whereas the central part is constituted by monohydrate. This finding leads some authors to believe that the initial precipitation is always of the same dihydrate found in oxaluria which gradually loses water becoming a monohydrate.[5]

Others[4] do not agree with this explanation of the finding of mono- and dihydrates in the same calculus, believing that both forms are precipitated independently and simultaneously but not changing from one into the other.

There are references in the literature which differentiate the calcium oxalate crystals found in oxaluria from the ones observed in calcium oxalate stones.[6, 7] However, more accurate methods of observation and analysis point to the contrary, identifying the octahedral crystals of the oxaluria as the same dihydrate found in calculi, pure or associated with the monohydrate.[4]

It has also been demonstrated that magnesium, besides influencing the oxalate output, plays a considerable role in its solubility, increasing it more than any other ion.[3]

In this investigation we tried to correlate the urinary excretion of calcium oxalate with the recurrent formation of oxalate stones and the presence of persistent crystaluria of calcium oxalate. Observations were also undertaken to check clinically the capability of oral administered magnesium to control persistent oxalate crystalluria and recurrent formation of oxalate stones.

The method used to determine oxalic acid in

[1] Archer, H. E., Dormer, A. E., Sowen, E. F. and Watts, R. W. E.: Studies on urinary excretion of oxalate by normal subjects. Clin. Sc., **16:** 405–411, 1957.

[2] Hammarsten, G.: In: Etiological Factors in Renal Lithiasis. Springfield, Ill.: Charles C. Thomas, 1956.

[3] Hammarsten, G.: On calcium oxalate and its solubility in presence of inorganic salts with special reference to occurrence of crystaluria. Comptes rendus des travaux du Laboratoire Carlsberg, **17:** 1–85, 1929.

[4] Prien, E. L. and Frondel, C.: Studies in urolithiasis; composition of urinary calculi. J. Urol., **57:** 949–994, 1947.

[5] Tooborg-Jensen, A.: On concrements from urinary tract. Acta chir. scandinav., **55:** 473–486, 1941.

[6] Ord, W. M. and Shattock, S-G.: On the microscopic structure of urinary calculi of oxalate lime. Trans. Path. Soc., London, **46:** 91–132, 1945.

[7] Keyser, L.: The mechanism of the formation of urinary calculi. Ann. Surg., **77:** 710–722, 1923.

the urine was the one described by Archer and associates,[1] in which the oxalic acid is precipitated by calcium chloride in pH 5.0–5.2, the precipitate being centrifuged, washed and titrated with potassium permanganate.

TABLE 1

Case No.	Sex	24 hr. Output	Crystalluria
1	M	29.10	1+
2	M	44.42	0
3	M	46.37	3+
4	M	54.62	0–1+
5	M	22.28	3+
6	M	18.72	0
7	M	30.42	3+
8	M	32.87	3+
9	M	28.65	3+
10	M	18.12	0+
11	M	18.00	—
12	M	18.35	3+
13	M	10.46	0
14	M	13.15	1+
15	M	30.42	3+
16	M	33.32	—
17	M	13.06	0–1+
18	M	23.12	1+
19	M	107.41	2+
20	F	40.05	3+
21	F	71.58	3+
22	F	25.17	—
23	F	60.30	3+
24	F	25.74	—

TABLE 2

Case No.	Sex	Without Mg Oxide		With Mg Oxide	
		Output	Crystalluria	Output	Crystalluria
3	M	46.37	3+	25.46	0
5	M	22.28	3+	12.98	0
7	M	30.42	3+	12.16	0
12	M	18.35	3+	12.42	0
19	M	107.41	2+		
20	F	40.05	3+	25.27	0
21	F	71.58	3+	22.67	0–1+
23	F	60.30	3+	47.02	0
4	M	54.62	0–1+	13.92	0
8	M	32.87	3+	17.18	0
15	M	30.42	3+		

TABLE 3

Case No.	Sex	Output Before Treatment	Output After Treatment	% Difference With Treatment
3	M	46.37	25.46	45.09
5	M	22.28	12.92	41.74
7	M	30.42	12.16	60.03
12	M	18.35	12.42	32.32
4	M	54.62	13.92	74.51
8	M	32.87	17.18	47.73
20	F	40.05	25.25	36.90
21	F	71.58	22.67	68.33
23	F	60.30	47.02	22.02

Other methods were tried, but did not prove practical.

All determinations were performed in three samples to one of which was added 0.5 cc oxalic acid solution 0.1 n. or 2.251 mg.; the recovery varied between 2.093 and 2.503 mg. or 93 and 111.2 per cent with a weight average of 2.252 mg. or 100.06 per cent; the standard deviation was 4.123.

In order to determine our normal levels once the technique had been standardized, seven males and seven females of varying ages were chosen, kept on regular diets and ascertained not to have clinical or laboratory evidence of genitourinary disease. On the males the 24 hour urinary output varied between 35.70 and 11.20 mg. with an average of 22.77 mg. per 24 hours. On the females the levels varied between 14.43 and 20.27 mg. per 24 hours with an average of 17.84 mg. Statistical analysis of these data was undertaken by Dr. A. Scorzelli Jr. for whose help the authors are greatly indebted and wish to acknowledge their thankfulness.

The difference between the average figures for normal males and females is 4.93 and the significance test (Student-Fisher) shows to be only casual the difference between the two sexes,* the normal average for men and women being 20.31 mg. per 24 hours.

Twenty-four patients (19 males and 5 females) with recurrent or bilateral lithiasis were studied, all with pure oxalate stones or with an overwhelming predominance of oxalate by quantitative chemical analysis. In these cases the oxalate crystalluria was continuous or frequent in micro-

* P level = 0.05, t test = 1.41 for 12 degrees

scopic examinations of the sediment in freshly voided urine specimens of the males or catheter specimens of the females, the examinations being performed at 2 to 4 day intervals during several weeks. All patients had normal pH curves of the urine. None had laboratory evidence of hyperparathyroidism; however, cases 2 and 3 had considerable hypercalcuria ranging from 246, 252, 279 mg. per 24 hours and 228, 292 and 400 mg. per 24 hours, respectively.

Table 1 gives the figures of the 24 hour output in milligrams found in these cases and the severity of the crystalluria.

The 24 hour output in these cases showed a lesser variation for the females, even when the figure 107.41 found in one of the men was discarded from the data analyzed: the average output for the men with oxalate stones became 26.97 while for the women it was 44.57. The difference between the averages for both sexes (17.60) was significant at a P level of 0.05, when $t = 2.44$, pointing to higher average levels among the women with lithiasis.

If the average output of normal cases for each sex is compared separately with the average output found in the cases of same sex with lithiasis, one finds that the difference (4.21) was not significant among men *, while among the women (26.72) it was highly significant with $t = 3.47$.

Considering the results of both sexes combined, the average output was 30.80 which is definitely significant when compared to the normal average (20.31 mg./24 hours).

Eleven of these cases were given 0.15 gm. magnesium oxide 3 times daily for varying periods, the 24 hour urinary output of oxalic acid determined after at least 14 days of treatment, while the microscopic examination of the urinary sediment in freshly obtained samples was done at 2-4 day intervals.

Table 2 gives the findings in this group. The significance test of these results was equally analyzed. The difference between the determinations in each individual, before and after the use of magnesium oxide, was established and the per cent relationship of this difference in relation to the initial value (before treatment) was established (table 3).

The average of these differences was 47.63 which was highly significant ($P = 0.05$, $t = 5.71$ for 8 degrees) the decrease in output being not casual.

Crystalluria was present in every case before treatment, its severity seeming independent from the greater or lesser excretion of oxalic acid, as it was 3 plus in case 12 which showed the lowest output as well as in case 21 which showed the highest among those analyzed. The use of magnesium oxide, while only reducing significantly the excretion of oxalic acid, eliminated the crystaluria in practically all cases studied. As oxalate was still being excreted, one can speculate that either at the treatment level it would not precipitate or that some new factor would render it more soluble.

In conclusion it seems that in the cases of recurrent oxalate lithiasis studied: a) there is a significant increase in the oxalic acid excretion per 24 hours, which b) corresponds to a persistently high oxalate crystalluria; c) that the increase is more marked in women than in men; d) that the use of magnesium oxide reduces considerably the excretion of oxalic acid and e) practically eliminates the oxalate crystaluria in these cases.

The wide variations found in the 24 hour excretion on the cases observed have been explained by other authors[2, 3] and should be taken in consideration when undertaking metabolic studies of oxalic acid.

Rua Assembleia, 51, Rio de Janeiro, Brazil

* The difference of 4.21 was not significant as $t = 0.82$, which points to casual variation.